IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

HERON THERAPEUTICS, INC.,	)	
Plaintiff,	)	C.A. No. 24-1363-WCB
v.	)	
SLAYBACK PHARMA LLC and AZURITY PHARMA INDIA LLP'S f/k/a SLAYBACK PHARMA INDIA LLP's AND AZURITY PHARMACEUTICALS, INC.,	)	
Defendants.	)	

DEFENDANTS SLAYBACK PHARMA LLC'S, AZURITY PHARMA INDIA LLP'S AND AZURITY PHARMACEUTICALS, INC.'S INVALIDITY CONTENTIONS

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I. INTRODUCTION

Pursuant to the Scheduling Order entered in C.A. No. 24-1363 (WCB) (D.I. 21) on January 8, 2025, Defendants Slayback Pharma LLC, Azurity Pharma India LLP f/k/a Slayback Pharma India LLP, and Azurity Pharmaceuticals, Inc. (collectively "Azurity" or "Defendants"), by and through its attorneys, provide their Invalidity Contentions with respect to the asserted claims of U.S. Patent Nos. 12,115,254 ("the '254 patent"), and 12,115,255 ("the '255 patent") (collectively "the Two New OB Patents") which were asserted by Heron Therapeutics, Inc. ("Heron" or "Plaintiff") in its Complaint.

Heron has asserted that Defendants' 505(b)(2) New Drug Application No. 218754 ("Azurity's Proposed Product") infringes claims 1, 5-7, 9, 11, 15, 19-22, 24, 26-27, and 29 of the '254 patent; and claims 1, 5-11, 13, and 16-30 of the '255 patent (collectively "the Asserted Claims of the Two New OB Patents").

Defendants contend that all Asserted Claims of the Two New OB Patents are invalid under one or more of 35 U.S.C. §§ 102, 103, or 112, as described in further detail below. These Invalidity Contentions may be asserted in the alternative and do not constitute any concession by Defendants for purposes of claim construction or infringement. *See* Fed. R. Civ. P. 8(d).

II. RESERVATION OF RIGHTS

Defendants' Invalidity Contentions are based on information reasonably available at this time with respect to the Two New OB Patents, and are necessarily preliminary and may require subsequent amendment, modification, and/or supplementation including as required and permitted by Local and Federal Rules. Moreover, fact discovery is ongoing, and Defendants have not obtained deposition testimony of any of the named inventors of any of the Two New OB Patents or any third party. Defendants expect further discovery will reveal additional prior art, including

related disclosures and corresponding evidence for many of the prior art references identified below. As such, Defendants have not yet completed their investigation, discovery or analysis of matters relating to the validity or enforceability of the Two New OB Patents, including, without limitation, invalidity due to on-sale statutory bars, public use statutory bars or improper inventorship, or unenforceability. The disclosures herein are not and should not be construed as a statement that no other persons have discoverable information, that no other documents, data compilations, and/or tangible things exist that Defendants may use to support their claims or defenses, or that no other legal theories or factual bases will be pursued. Accordingly, Defendants reserve the right to amend, modify and/or supplement its Invalidity Contentions based on, among other things, amendments, modifications or supplements to Plaintiff's infringement contentions, further investigation, fact or expert discovery and/or evaluation of the scope and content of the prior art, disclosure of the parties' claim constructions, an order construing the Two New OB Patents, or any other basis contemplated by the Federal Rules of Civil Procedure, the Court's Local Rules, the Court's forthcoming Scheduling Order, any agreement of the parties, and any other applicable order entered by the Court.

Further, Defendants' Invalidity Contentions are provided without prejudice to the rights of Defendants to introduce at trial expert opinions relating to currently known facts and subsequently discovered facts, and any subsequently discovered evidence to support Defendants' arguments or rebut Plaintiff's arguments; and to produce and introduce at trial all evidence, wherever discovered, relating to the proof of currently known and subsequently discovered facts.

Defendants' Invalidity Contentions do not indicate Defendants' position with regard to the proper claim construction of any term of the Two New OB Patents. Instead, because no claim construction order has been entered in this case, Defendants have made reasonable assumptions,

to the extent necessary and appropriate, with respect to the meaning of patent claim terms for the purpose of preparing these Invalidity Contentions. Defendants reserve the right to rely upon different meanings in the course of this litigation and to assert different meanings as appropriate in connection with any *Markman* procedures and proceedings, or any applicable meanings agreed to by the parties. Defendants further reserve the right to update these Invalidity Contentions following a *Markman* opinion adopting meanings that differ from those assumed by Defendants, or any other judicial clarification or alteration of the meaning of claim terms, and/or as otherwise authorized or permitted by the Local Rules and the Federal Rules of Civil Procedure.

Defendants' Invalidity Contentions should not be taken to mean that: (1) Defendants agree with Plaintiff's bases for infringement; (2) Defendants agree with Plaintiff regarding the scope of any of the Asserted Claims of the Two New OB Patents; (3) Defendants agree with Plaintiff's claim constructions advanced directly or implicitly by Plaintiff's Disclosure of Asserted Claims of the Two New OB Patents or in any other pleading, discovery request or response, or written or verbal communication with Defendants; (4) Defendants are precluded from propounding alternative claim constructions or requesting Plaintiff's actual claim construction positions in the future; or (5) Defendants agree or believes the claims at issue are amenable to a meaningful construction or satisfy the requirements of 35 U.S.C. § 112. Defendants expressly reserve the right to propose and advocate for alternative constructions to those apparently advocated by Plaintiff. In addition, nothing in Defendants' Invalidity Contentions shall be treated as an admission that Azurity's Proposed NDA Product meets any limitation of the Two New OB Patents. Any attempt by Plaintiff to use these Invalidity Contentions to support any allegation of infringement would be misleading, false, and factually inaccurate.

The Invalidity Contentions set forth herein are based on the alleged effective filing date of the Two New OB Patents as indicated on the face of the patents. To the extent Plaintiff asserts entitlement to effective filing dates prior to the filing of the applications that ultimately issued as the Two New OB Patents, Defendants reserve the right to amend these Invalidity Contentions.

Regarding the prior art references discussed herein, Defendants have identified exemplary portions of the references that disclose the claimed limitations, though such portions are not meant or intended to be exhaustive. The references may contain additional support for particular claim limitations. A person of ordinary skill in the art ("POSA") would have understood and interpreted the cited passages in the context of the prior art references as a whole, as well as in the context of the state of the art. In addition, the cited references may be combined and modified in a number of ways to achieve the compositions and methods recited in the claims. Defendants expressly reserve the right to rely on uncited portions of the prior art references, other documents, and expert testimony to provide further context or to aid in the understanding of the cited portions of the references.

Defendants are not aware of how Plaintiff may attempt to distinguish the prior art cited herein, and Defendants reserve the right to identify other references that would have supplied the allegedly missing elements to render the claims of the Two New OB Patents obvious or to counter alleged evidence of secondary indicia of non-obviousness and to provide additional factual and expert evidence to rebut any arguments Plaintiff may make in response to the prior art Defendants present. Plaintiff has not identified what limitations of the claims of the Two New OB Patents it alleges were not known to one skilled in the art at the time of the alleged inventions recited in the Two New OB Patents. For any claim limitation that Plaintiff alleges is not disclosed in a prior art reference, Defendants reserve the right to assert that such limitation is either inherent in the

reference or would have been obvious to one skilled in the art in light of the same, or that the limitation is disclosed in one or more prior art references and in combination would have rendered the Two New OB Patents obvious.

Through these Invalidity Contentions, Defendants do not intend to disclose information that is protected by the attorney-client privilege, the attorney work-product immunity, the common-interest privilege, or any other applicable privilege or immunity. To the extent that Defendants inadvertently disclose information that may be protected from discovery under the attorney-client privilege, the attorney work-product immunity, the common-interest privilege, or any other applicable privilege or immunity, such inadvertent disclosure does not constitute a waiver of any such privilege or immunity.

The contentions set forth below are provided by Defendants without waiver of Defendants' right to: (1) object on any ground including, without limitation, privilege, relevance or materiality, to the use of any statement herein in this or any other action; (2) object to any request for further discovery relating to the subject matter of the statements herein; or (3) revise, correct, supplement, or clarify any of the statements provided herein.

Defendants further reserve the right to supplement their production should Defendants later locate, identify, or otherwise appreciate additional responsive documents. Defendants additionally incorporate, in full, all prior art references cited in the Two New OB Patents as well as any related patents and/or applications and their respective prosecution histories, whether the related patents and/or applications were filed in the United States or in a foreign country. Defendants further incorporate by reference any and all grounds for invalidity submitted by any party in any *inter partes* review or any other administrative proceeding, including before the USPTO or any foreign

equivalent agency, including any and all references cited or relied upon therein. Subject to the foregoing, Defendants hereby submit their Invalidity Contentions which are fully explained below.

III. THE TWO NEW OB PATENTS

A. The '254 Patent

The '254 patent, entitled "Methods of Use of Emulsion Formulations of an NK-1 Receptor Antagonist," issued on Oct. 15, 2024, from U.S. Application No. 18/408,486 ("the '486 application"). The '486 application was filed on Jan. 9, 2024, as a continuation of U.S. Application No. 18/535,853 ("the '853 application"). The '853 application was filed on Dec. 11, 2023, as a continuation of U.S. Application No. 17/180,593 ("the '593 application"), filed on Feb. 19, 2021, now U.S. Pat. No. 11,878,074 ("the '074 patent"), which is a continuation of U.S. Application No. 16/820,311 ("the '311 application"), filed on Mar. 16, 2020, now U.S. Pat. No. 11,173,118 ("the '118 patent"), which is a continuation of U.S. Application No. 15/965,638 ("the '638 application"), filed on Apr. 27, 2018, now U.S. Pat. No. 10,624,850 ("the '850 patent"), which is a continuation of U.S. Application No. 15/012,532 ("the '532 application"), filed on Feb. 1, 2016, now U.S. Patent No. 9,974,742 ("the '742 patent").

B. The '255 Patent

The '255 patent, entitled "Methods of Use of Emulsion Formulations of an NK-1 Receptor Antagonist," issued on Oct. 15, 2024, from U.S. Application No. 18/418,030 ("the '030 application"). The '030 application was filed on Jan. 19, 2024, as a continuation of the '853 application. *See*, Section IV. A.

IV. IDENTIFICATION OF ASSERTED CLAIMS

On January 7, 2025, Heron provided its Disclosure of Asserted Claims of the Two New OB Patents pursuant to the Scheduling Order. Heron has asserted the following claims of the Two

New OB Patents:

Patent	Asserted Claims
The '254 patent	1, 5-7, 9, 11, 15, 19-22, 24, 26-27, and 29
The '255 patent	1, 5-11, 13, and 16-30

V. IDENTIFICATION OF PRIOR ART

A. Effective Filing Dates

The '254 and '255 patents share a common lineage and claim priority to the '532 application filed on February 1, 2016. Accordingly, the applicable effective filing date for the '254 and '255 patents is no earlier than February 1, 2016. Because the '532 application was filed after March 16, 2013, the AIA versions of 35 U.S.C. §§ 102, 103, 112 apply.

B. Listing of the Prior Art

Defendants reserve the right to challenge the earliest claimed effective filing dates and critical date of the Two New OB Patents. At this time, Defendants contend that at least the following prior art renders invalid, either alone or in combination, all Asserted Claims of the Two New OB Patents as set forth more fully below:

Prior Art	Short Cite
R. P. Bagwe, *et al.*, "Improved Drug Delivery Using Microemulsions: Rationale, Recent Progress, and New Horizons", *Critical Reviews in Therapeutic Drug carrier Systems* **2001**, *18*, 77-140.	Bagwe
Max T. Baker and Mohamed Naguib, "The Challenges of Formulation", *Anesthesiology,* **2005**, *103*, 860-876.	Baker
S. Benita and M. Y. Levy, "Submicron Emulsions as Colloidal Drug Carriers for Intravenous Administration: Comprehensive Physicochemical Characterization", *Journal of Pharmaceutical Sciences* **1993**, *82*, 1069-1079.	Benita

Prior Art	Short Cite
Michael Billany, "Suspensions and Emulsions", In: *Pharmaceutics: The Science of Dosage Form Design*, Ed. Michael E. Aulton, 2nd ed., Edinburgh: Churchill Livingstone, 2002, 334-359.	Billany
Begoña Brime, *et al.*, "Amphotericin B in Oil-Water Lecithin-Based Microemulsions: Formulation and Toxicity Evaluation", *J. Pharm. Sci.* **2002**, *91*, 1178-1185.	Brime
Joanne Broadhead and Mark Gibson, "Parenteral Dosage Forms", In: *Pharmaceutical Preformulation and Formulation*, Ed. Mark Gibson, 2nd ed., Informa Healthcare USA, Inc., NY, 2009, 195-226.	Broadhead
John B. Cannon, Yi Shi, and Pramod Gupta, "Emulsions, Microemulsions, and Lipid-Based Drug Delivery Systems for Drug Solubilization and Delivery – Part I: Parenteral Applications", In: *Water-Insoluble Drug Formulation*, Ed. R. Liu, 2nd ed., Boca Raton: CRC Press, 2008, 195-226.	Cannon
S. Cheng Yang and Simon Benita, "Enhanced Absorption and Drug Targeting by Positively Charged Submicron Emulsions", *Drug Development Research* **2000**, *50*, 476-486.	Cheng Yang
Ching-Chiang Su, *et al.*, "Drug solubility and solubilization" In: *Pharmaceutical Dosage Forms: Parenteral Medications*, Eds. Sandeep Nema and John D. Ludwig, 3rd ed., Volume 1, Formulation and Packaging, Informa Healthcare, 2010, 134-157.	Ching-Chiang Su
Prescribing Information of CLEVIPREX (clevidipine) injectable emulsion, for intravenous use, Fresenius Kabi, Dec. 2011.	Cleviprex label
L.C. Collins-Gold, *et al.*, "Parenteral emulsions for drug delivery", *Adv. Drug Deliv. Rev.* **1990**, *5*, 189-208.	Collins-Gold
Julian Eastoe, *et al.*, "Microemulsions", In: *Encyclopedia of Colloid and Interface Science*, Ed. T. Tadros, Springer, Berlin, Heidelberg, 2013, 688-729.	Eastoe
Prescribing Information of EMEND® (aprepitant capsules), Merck Sharp & Dohme Corp., Dec. 2012.	Emend label
R. Hargreaves, *et al.*, "Development of aprepitant, the first neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting", *Ann. N.Y. Acad. Sci*, **2011**, *1222*, 40-48.	Hargreaves
Ketan Hippalgaonkar, *et al.*, "Injectable Lipid Emulsions – Advancements, Opportunities and Challenges", *AAPS PharmSciTech.* **2010**, *11*, 1526-1540.	Hippalgaonkar

Prior Art	Short Cite
Barkat Ali Khan, *et al.*, "Basics of pharmaceutical emulsions: A review", *African J. of Pharma. and Pharmacol.* **2011**, *5*, 2715-2725.	Khan
V. Klang and C. Valenta, "Lecithin-based nanoemulsions", *J. Drug Del. Sci. Tech.* **2011**, *21*, 55-76.	Klang
John Klier, *et al.*, "Properties and Applications of Microemulsions", *Adv. Mater.* **2000**, *12*, 1751-1757.	Klier
Ram I. Mahato and Ajit S. Narang, "Emulsions", In: *Pharmaceutical Dosage Forms and Drug Delivery*, Eds. Ram I. Mahato and Ajit S. Narang, 2nd ed., CRC Press, Taylor & Francis Group, 2012, 255-268.	Mahato
Gilberte Marti-Mestres and Françoise Nielloud, "Main Surfactants Used in the Pharmaceutical Field", In: *Pharmaceutical Emulsions and Suspensions*, Eds. Françoise Nielloud and Gilberte Marti-Mestres, New York, Marcel Dekker, Inc., 2000, 1-18.	Marti-Mestres
Vandana B. Patravale and Abhijit A. Date, "Microemulsions: Pharmaceutical Applications", In: *Mircoemulsions: Background, New Concepts, Applications, Perspectives*, Ed. Cosima Stubenrauch, 1st ed., Wiley-Blackwell, 2009, 259-301.	Patravale
Joanna Rossi and Jean-Christophe Leroux, "Principles in the Development of Intravenous Lipid Emulsions", In: *Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery*, Ed. Kishor M. Wasan, John Wiley & Sons, 2007, 88-123.	Rossi
Jean-Louis Salager " Emulsion Properties and Related Know-how to Attain Them", In: *Pharmaceutical emulsions and suspension*, Eds. Françoise Nielloud and Gilberte Marti-Mestres, New York, Marcel Dekker, Inc., 2000, 73-125.	Salager
Shailesh K. Singh and Venkatesh Naini, "Homogenization and Homogenizers", In: *Encyclopedia of Pharmaceutical Technology*, Ed. J. Swarbrick, Informa Healthcare USA, Inc., New York, 2007, 1996-2003.	Singh
Erik Sjögren, *et al.*, " In silico predictions of gastrointestinal drug absorption in pharmaceutical product development: Application of the mechanistic absorption model GI-Sim", *European Journal of Pharmaceutical Sciences* **2013**, *49*, 679-698.	Sjögren

Prior Art	Short Cite
Charalambos Tsagogiorgas, *et al.*, "Buccal absorption of propofol when dosed in 1-perfluorobutylpentane to anaesthetised and conscious Wistar rats and Göttingen mini-pigs", *European Journal of Pharmaceutics and Biopharmaceutics* **2001**, *85*, 1310–1316 .	Tsagogiorgas
C. Washington, "Stability of lipid emulsions for drug delivery", *Advanced Drug Delivery Reviews* **1996**, *20*, 131-145.	Washington
Yan Weng, *et al.*, "Formulation, preparation, and stability of intravenous bufadienolides-loaded lipid microspheres", *Eur. J. Lipid Sci. Technol.* **2012**, *114*, 1154-1164.	Weng
Zhou Wei, *et al.*, "Preparation of Aprepitant Emulsion for Intravenous Injection ", *Chinese Journal of Pharmaceuticals* **2012**, *43*, 1003-1006.	Zhou 2012
CN 102379845 (published on March 21, 2012)	Zhou
US 2001/0007663 (published on July 12, 2001)	"the '663 publication"
US 2007/0071777 (published on March 29, 2007)	"the '777 publication"
US 2007/0249520 (published on October 25, 2007)	"the '520 publication"
US 2011/0038925 (published on February 17, 2011)	"the '925 publication"
US 2013/0236501 (published on September 12, 2013)	"the '501 publication"
US 2013/0317016 (published on November 28, 2013)	"the '016 publication"
WO 2007/147160A2 (published on December 21, 2007)	WO '160
WO2012051116A1 (published on April 19, 2012)	WO '116

C. <u>Background on the Scope and Content of the Prior Art</u>

By way of example only, Defendants summarize the scope and exemplary content of the prior art references disclosed above as follows:

1. **Bagwe**

Bagwe is a journal article that was published in 2001 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Bagwe are R. P. Bagwe, J. R. Kanicky, B. J. Palla, P. K. Pantanjali, and D. O. Shah.

Bagwe discusses microemulsions, disclosing that "[m]icroemulsions require a relatively large amount of surfactant in order to stabilize the large interfacial area created by the nanodroplets. Microemulsions also often require the addition of cosurfactants such as alcohols, amides, and sulphoxides to attain an appropriate fluidity or viscosity of the interface." Bagwe at 80. Bagwe discloses that one of the most "important conditions for producing microemulsions" is a "sufficiently high concentration (10-40%) of surfactant to cover the newly created surface within the microemulsion." *Id.* at 89. Bagwe further discloses that "…the choice of a surfactant system is very important in controlling the required surfactant concentration." *Id.* at 80. Bagwe teaches that "[t]he surfactants used for pharmaceutical microemulsions should be nonirritating. Phospholipids, particularly lecithin, offer a possible nontoxic alternative emulsifier for parenteral use." *Id.* at 101. Further explaining, "[t]he most commonly employed components are cholesterol and lecithin, which are biocompatible and hence eliminate toxicity concerns." *Id.* at 83.

2. **Baker**

Baker is a journal article that was published in 2005 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Baker are Max T. Baker and Mohamed Naguib.

Baker discloses that propofol emulsion formulations have distinct clinical advantages over other formulations. For example, propofol administered in lipid emulsion was demonstrated to be

more potent and rapid acting than equivalent doses of propofol administered by a method involving a lipid-free vehicle. Baker at 862.

Additionally, Baker states major factors that govern this process for any lipophilic drug are the drug concentration gradient, the partition coefficient, the drug diffusivity in both phases, and the interfacial area of the drug-containing oil droplets. *Id.* The total interfacial surface area in an emulsion – dependent on the size and number of oil droplets – is a highly important factor in the rate of drug release from a drug containing droplet. A reduction in droplet size from 1.0 µm in diameter to 0.1 µm results in an approximately 42-times increase in the oil-water surface area, and the latter allows for a more rapid rate of release of propofol to the blood. *Id.*

3. <u>Benita</u>

Benita is a journal article that was published in 1993 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Benita are S. Benita and M. Y. Levy.

Benita discloses emulsions for intravenous administration, disclosing that "[t]he emulsions must be sterile, isotonic, nonpyrogenic, nontoxic, biodegradable, and *stable, both physically and chemically*." Benita at 1069 (emphasis added). Benita teaches that "[s]pecial attention should be given to two major excipients in the emulsions formulation – the oil and the emulsifier(s)" disclosing that "[i]n previous studies, the oil phase of the emulsion was based mainly on long-chain triglycerides (LCT) from vegetable sources (soybean, safflower, and cottonseed oils)" and "[t]he emulsifiers most frequently used in parenteral emulsion formulations are phospholipids (generally from egg yolk sources)…" *Id.* at 1070. Benita discloses that "[a]dditives are needed to adjust the emulsion to physiological pH and tonicity" further disclosing that "[t]he initial pH of the emulsion may decrease progressively with time. However, this pH decrease can be controlled

by adjusting the initial pH of the emulsion. Provided that the initial adjusted pH is satisfactory, the rate of hydrolysis of phospholipids and triglycerides may be minimized. Therefore, the pH of the emulsion should be monitored continuously over the entire shelf life of the emulsion to detect detrimental free fatty acid formation." *Id.* at 1073.

4. <u>Billany</u>

Billany is a chapter from a textbook that was published in 2002 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The author of Billany is Michael Billany.

Billany discloses that "[t]he inclusion of an emulsifying agent or agents is necessary to facilitate actual emulsification during manufacture, and also to ensure emulsion stability during the shelf-life of the product." Billany at 347. Billany divides emulsifying agents and emulsifiers into categories of anionic surfactants, cationic surfactants, non-ionic surfactants, and amphoteric surfactants and lists lecithin as an amphoteric surfactant. *Id.* Billany further discloses that "[t]he inclusion of surface-active agents … may also help to prevent crystal growth." *Id.* at 337.

5. <u>Brime</u>

Brime is a journal article that was published in 2002 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Brime are Begoña Brime, Marco A. Moreno, Gloria Frutos, Ma. Paloma Ballesteros, and Paloma Frutos.

Brime discusses the formulation of oil-water lecithin-based microemulsions of Amphotericin B. Brime discloses that Amphotericin B is "practically insoluble in water." Brime at 1178. Brime further discloses the formulation of different microemulsions of Amphotericin B containing 15-20% (w/w) of Brij® 96V and 10% (w/w) of lecithin as the emulsifiers. *Id.* at 1182,

Table 1. Brime discloses "[i]t was necessary to keep the amount of lecithin used in the different formulations over 10% (w/w), due to its importance for the incorporation of AmB [Amphotericin B]." *Id.*

6. <u>Broadhead</u>

Broadhead is a chapter from a textbook that was published in 2009 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Broadhead are Joanne Broadhead and Mark Gibson.

Likewise, Broadhead discloses that the use of a surfactant is one strategy for developing parenteral formulations of drugs with low solubility. Broadhead at 331. Broadhead further mentions that there are a few i.v. products — *e.g.*, Cordarone i.v. and Etoposide i.v. — that contain significant levels of surfactant (polysorbate 80), 10% and 8%, respectively. *Id.* Additionally, Aquasol A (vitamin A palmitate as retinol) which is used for intramuscular administration, is reported to contain 12% polysorbate 80. *Id.*

7. <u>Cannon</u>

Cannon is a chapter from a textbook that was published in 2008 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Cannon are John B. Cannon, Yi Shi, and Pramod Gupta.

Cannon discloses that several factors contribute to the physical stability of an emulsion. Cannon at 215. ("Some of the factors that affect the physical stability of emulsions include the type and concentration of surfactant used to stabilize the emulsion, the phase volume ratio (i.e., ratio of oil to aqueous phase), droplet size, compatibility of drug and excipients with the emulsion, and storage condition of the emulsion.") Cannon further discloses that the use of an appropriate emulsifying agent can improve the stability of an emulsion. *Id.* at 216. ("Use of the appropriate

emulsifying agent improves the physical stability of an emulsion by one or more of the following mechanisms: reducing interfacial tension, preventing coalescence (by the emulsifying agent being adsorbed around the droplets), imparting electrical potential on the droplets (which favors their repulsion), and/or increasing viscosity (which minimizes droplet interaction).") Cannon teaches that "[t]he most commonly used surfactant in parenteral products is lecithin [phosphatidylcholine (PC)], which is a natural emulsifying agent derived from egg yolk or soybean." *Id.* at 198. Cannon further teaches that there is an optimum surfactant concentration range and that too much or too little surfactant will result in an unstable emulsion. *Id.* at 216. ("Whereas an inadequate concentration of surfactant will do little to prevent coalescence, undue increase in its concentration often leads to problems like increased drug instability and difficulty in administration. Excess surfactant molecules will tend to self-associate, forming micellar or lamellar structures, which may compromise the effectiveness of the emulsion.")

8. <u>Cheng Yang</u>

Cheng Yang is a journal article that was published in 2000 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Cheng Yang are Shi Cheng Yang and Simon Benita.

Cheng Yang discusses methods of emulsion preparation and, discloses that "[m]ethods of submicron emulsion preparation have been described in detail." Cheng Yang at 477. Cheng Yang further discloses a method of emulsion preparation wherein, "the required amount of drug is dissolved in the oil phase and mixed thoroughly with the water phase. The mixture is emulsified with a high shear homogenizer at 15-20,000 rpm for a short time (1-5 min). The coarse oil-in-water emulsion formed is then homogenized through a high-pressure homogenizer (6 cycles at 800

bar). The resulting submicron emulsion preparation is filtered through a 0.45 μm membrane…" *Id.*

9. <u>Ching-Chiang Su</u>

Ching-Chiang Su is a chapter from a textbook that was published in 2010 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Ching-Chiang Su are Ching-Chiang Su, Lan Xiao, and Michael Hageman.

Ching-Chiang Su discusses emulsions and discloses that "[b]ecause of the numerous small droplets, the surface area to volume ratio of microemulsions are very high and it forms easily because of the low surface tension, typically due to high levels of surface active species." Ching-Chiang Su at 150.

10. <u>Cleviprex label</u>

Cleviprex label is the prescribing information of clevidipine injectable emulsion (for intravenous use) that was published in Dec. 2011 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply.

Cleviprex label states that clevidipine is "practically insoluble in water and is formulated in an oil-in-water emulsion." Cleviprex label at DESCRIPTION. The composition contains, *inter alia*, 0.5 mg/mL of clevidipine and 12 mg/mL egg yolk phospholipids – which amounts to an emulsifier to clevidipine ratio of 24:1. *Id.* The Description further states that Cleviprex emulsion has a pH of 6.0 –8.0.

11. <u>Collins-Gold</u>

Collins-Gold is a journal article that was published in 1990 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Collins-Gold are L.C. Collins-Gold, R.T. Lyons, and L.C. Bartholow.

Collins-Gold discusses parenteral emulsions for drug delivery. Collins-Gold reports that "[w]hile a wide variety of surfactants are available for industrial manufacturing of foods, cosmetics, insecticides, paints, detergents and so forth, relatively few are approved for i.v. administration. Natural phosphatides, principally from egg yolk or soybean, are in most widespread use." Collins-Gold at 192. Collins-Gold further discloses that "[f]or parenteral use, a droplet mean diameter of less than 1 μm is highly desirable." *Id.* at 193. "Furthermore, droplets larger than 5 μm are capable of forming emboli in small capillaries such as in the lungs." *Id.* at 195. Collins-Gold discloses that droplet size can be decreased by increasing surfactant concentration, however, after a certain point, increasing the surfactant concentration further will result in increased viscosity. *Id.* at 194, Table 1.

12. <u>Eastoe</u>

Eastoe is a chapter from a textbook that was published in 2013 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Eastoe are Julian Eastoe, Marios Hopkins Hatzopoulos, and Rico Tabor.

Eastoe discloses that "[m]icroemulsions may be considered as a subset of emulsions, exhibiting certain unique properties." Eastoe at 688. Eastoe further discloses that "[e]mulsions are systems of [] at least one fluid dispersed in another fluid: emulsions may be called macro-, mini-, nano-, and microemulsions." *Id.* at 689.

13. <u>Emend label</u>

Emend label is the prescribing information of aprepitant that was published in Dec. 2012 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply.

The Emend label states that aprepitant is practically insoluble in water and is sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile. Emend label at 12. Emend label further reports that the mean absolute oral bioavailability of aprepitant is only about 60 to 65% when given at the recommended dose range of 80-125 mg. Emend label at 13.

Emend label also mentions that aprepitant is used for the prevention of nausea and vomiting, including Chemotherapy Induced Nausea and Vomiting ("CINV") and Postoperative Nausea and Vomiting ("PONV"). *See e.g.*, Emend label at 1 (sections INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION). Emend label further discloses that the underlying nausea and vomiting can be associated with – (1) initial and repeat courses of highly emetogenic cancer chemotherapy or (2) initial and repeat courses of moderately emetogenic cancer chemotherapy. *Id.* at 1. The label also states that EMEND for Injection is a prodrug of aprepitant that can be used for the CINV regimen as an intravenous infusion. *Id.* at 2.

14. <u>Hargreaves</u>

Hargreaves is a journal article that was published in 2011 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Hargreaves are Richard Hargreaves, Juan Camilo Arjona Ferreira, David Hughes, Jos Brands, Jeff Hale, Britta Mattson, and Sandy Mills.

Hargreaves discloses the history and development of aprepitant for the prevention of CINV. Hargreaves at 40, 44, 46. Hargreaves mentions that aprepitant is the first and, as of the publication, the only NK-1 receptor antagonist available on the market for the prevention of acute and delayed CINV. *Id.* at 40. Hargreaves discloses that aprepitant was originally approved by the FDA as an oral dosage form. *Id.* at 44. Subsequently a water-soluble form of aprepitant – fosaprepitant – was developed as a prodrug that converts to aprepitant *in vivo*. *Id.* at 44, 46.

Hargreaves also explains that an injectable form of aprepitant was thought to be convenient because the availability of both oral and intravenous formulations would increase the delivery options available to oncologists and patients and provide maximum clinical dosing flexibility. *Id.* at 44.

15. <u>Hippalgaonkar</u>

Hippalgaonkar is a journal article that was published in 2010 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Hippalgaonkar are Ketan Hippalgaonkar, Soumyajit Majumdar, and Viral Kansara.

Hippalgaonkar discusses injectable lipid emulsions. Hippalgaonkar discloses that "[t]he choice of emulsifier is driven by its toxicity profile, intended site of delivery, and stabilizing potential." Hippalgaonkar at 1529. Additionally, "[n]atural lecithin, obtained from egg yolk, has been used extensively to stabilize injectable emulsions. These emulsifiers are bio-compatible, nontoxic, and are metabolized like natural fat." *Id.* at 1529. Hippalgaonkar further discloses that "[e]mulsifiers stabilize emulsions by reducing the interfacial tension of the system and providing enough surface charge for droplet-droplet repulsion." *Id*. Hippalgaonkar teaches that "[z]eta potential … is a useful parameter for stability assessment [of emulsions]. A number of factors such as pH, ionic strength, type and concentration of emulsifiers and presence of electrolytes can affect the zeta potential of the system. A zeta potential value of ±25 mV has been suggested to produce a stable emulsion." *Id.* at 1532. Hippalgaonkar also teaches the significance of droplet size in emulsions. *Id.* at 1537. ("[I]n particular type and concentration of lipid and emulsifier used, can significantly affect the droplet size … larger sized droplets (>than 250 nm compared to <100 nm) were cleared faster … compared to small sized emulsion, large size emulsions were rapidly eliminated from the blood circulation … [and] emulsions with droplet size larger than 200 nm

effectively inhibited drug penetration into [various organs] indicating size controlled disposition in the body.") Hippalgaonkar further discloses that a decrease in "the emulsifier concentration … would lead to an increase in the surface tension and an increase in the droplet size." *Id.* at 1532. Additionally, droplet size was also known to directly impact "toxicity and stability of the emulsion system" and the prior art recognized "droplet size and distribution" as some of the most important characteristics of an injectable emulsion. *Id.* at 1531.

16. <u>Khan</u>

Khan is a journal article that was published in 2011 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Khan are Barkat Ali Khan, Naveed Akhtar, Haji Muhammad Shoaib Khan, Khalid Waseem, Tariq Mahmood, Akhtar Rasul, Muhammad Iqbal, and Haroon Khan.

Khan discloses that "[t]he amount of emulsifying agent is one of the most important factors having an influence on the emulsion stability. Emulsifier concentration has a great impact on emulsion stability. A concentration window existed, out of which the emulsion stability is quickly declined. At low emulsifier concentration, the emulsion is unstable because of agglomeration of the oil droplets. At high emulsifier concentration emulsion instability occurs because of rapid coalescence…" Khan at 2719.

17. <u>Klang</u>

Klang is a review article that was published in 2011 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Klang are V. Klang and C. Valenta.

Klang is a review article discussing lipid-based nanoemulsions, teaching that "[l]ecithin is perhaps the most widely used natural emulsifying agent and has been used in the food industry for centuries … Natural lecithins are among the safest emulsifying agents on the market and the

incidence of allergic reactions to lecithin is very rare." Klang at 58. Klang discloses various advantages of lipid-based emulsions as drug delivery systems, such as "high solubilizing capacity for lipophilic drugs," reproducibility, and sterilizability. *Id.* at 56. Klang discloses that "the negative surface potential of lecithin-stabilized nanoemulsions is markedly pH-dependent and can be improved by adjustment of the pH to alkaline." *Id.* at 70. Further teaching that the pH of the emulsion decreases during long-term observation and that "it is recommended to adjust the pH value right after production." *Id.* at 61. Klang discloses that for some emulsion systems the surfactant may be present in amounts of 20 to 50 wt %. *Id.* at 57. Further disclosing that "an increase in lecithin concentration leads to the production of smaller particles due to an increased surfactant to oil volume ratio, which in turn leads to enhanced physical stability." *Id.* at 64.

18. <u>Klier</u>

Klier is a journal article that was published in 2000 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Klier are John Klier, Christopher J. Tucker, Thomas H. Kalantar, and D. P. Green.

Klier discloses that "microemulsions often require high surfactant levels in order to provide sufficient interfacial coverage to completely microemulsify the required levels of ingredients, as well as to provide sufficient formulation stability to temperature and compositional changes to meet practical storage and use requirements." Klier at 1752.

19. <u>Mahato</u>

Mahato is a chapter from a textbook that was published in 2012 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Mahato are Ram I. Mahato and Ajit S. Narang.

Mahato discloses that "[microemulsions] often contain a high concentration of the emulsifier(s) and a cosolvent (such as ethanol)." Mahato at 257. Mahato further discloses that

"[e]mulsifying agents can be surfactants, hydrophilic colloids, or finely divided solid particles." *Id.* at 262. Mahato lists lecithin as a type of phospholipid that is commonly used as an emulsifying agent. *Id.* at 262.

20. <u>Marti-Mestres</u>

Marti-Mestres is a chapter from a textbook that was published in 2000 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1), and no exceptions under § 102(b) apply. The authors of Marti-Mestres are Gilberte Marti-Mestres and Françoise Nielloud.

Marti-Mestres discloses that in the pharmaceutical field surfactants are used especially as emulsifiers, solubilizers, and wetting agents. Marti-Mestres at 2.

21. <u>Patravale</u>

Patravale is a chapter from a textbook that was published in 2009 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Patravale are Vandana B. Patravale and Abhijit A. Date.

Patravale discusses pharmaceutical applications of microemulsions. Patravale discloses that microemulsions have a surfactant content of >10% and that emulsions contain between 1-20% surfactant. Patravale Table 9.1 at 260. Patravale further discloses that the "[c]hoice of the surfactant is also very critical for the formulation of microemulsions … Generally, surfactants of natural origin are preferred over synthetic surfactants, e.g. phospholipids are preferred over synthetic surfactants wherever possible." *Id.* at 263. Patravale mentions "[t]he excipients that are acceptable for parenteral delivery are as follows:

- *Surfactants:* Poloxamer 188, Lecithin, Tween 80, Tween 20, Span 80, Solutol HS 15, Cremophore® EL.
- *Co-surfactants:* Ethanol, Propylene glycol, Benzyl alcohol, Glycofurol, PEG 400.
- *Oils:* Castor oil, soybean oil, MCTs, Ethyl oleate, IPM, Vitamin E."

Id. at 282-283.

Patravale teaches that "[e]thanol at concentrations above 10% usually results in the pain on injection." *Id.* at 283. Patravale further teaches that "[i]n the case of lecithin-based microemulsions, adjustment of the initial pH at 7-8 is also important in order to minimize the hydrolysis of the phospholipids and the triglycerides to fatty acids, which can decrease the pH of the microemulsion and may affect the stability." *Id.* at 266.

22. <u>Rossi</u>

Rossi is a chapter from a textbook that was published in 2007 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Rossi are Joanna Rossi and Jean-Christophe Leroux.

Rossi teaches the development of intravenous lipid emulsions. Rossi discloses that "[t]he purpose of surfactants is to emulsify the oil phase and provide physical stability against flocculation and coalescence during storage, which may be for extended periods of time. Surfactants provide physical stability by reducing the oil-water interfacial tension and promoting droplet-droplet repulsion." Rossi at 110. Rossi further discloses that "[i]t is important to state that surfactants provide the emulsions … with kinetic stability, which delays the destabilization process … surface-active agents can provide stability for several years, which is long enough for the system to be useful for practical purposes." *Id.* at 90.

Rossi teaches that injectable emulsions commonly use lecithins as the emulsifying agent. *Id.* at 110. ("Injectable emulsions are frequently emulsified with natural lecithins obtained from either egg yolk or soybeans. These lipids are biocompatible and biodegradable, and have relatively good emulsifying properties.") Rossi also describes the use of HCl or NaOH for the purpose of adjusting the pH in the description under *Aqueous Phase*. *Id.* at 112.

Furthermore, Rossi discusses the pharmaceutical manufacturing steps for preparing an emulsion.

> "The first step in emulsion preparation is usually to dissolve the water-soluble components (isotonizing agent and preservatives) in the aqueous phase and the lipophilic compounds (drug and perhaps the antioxidant) in the oil phase. The emulsifier can be dispersed in either phase. Both phases are typically heated and agitated to facilitate the dispersion of the various components … The oil phase is then added to the aqueous phase … This premix stage produces a coarse emulsion … To produce emulsions with small droplet size, microfluidization or high-pressure homogenization is usually used … After the desired droplet size is achieved, the formulation is filtered to remove large droplets or debris, and sterilized. Sterilization can be achieved by autoclaving or by filtration through a 0.22 μm cartridge filter."

Id. at 113.

23. <u>Salager</u>

Salager is a chapter from a textbook that was published in 2000 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The author of Salager is Jean-Louis Salager.

Salager discusses certain emulsion properties, *e.g.*, type, drop size, stability, and viscosity with composition components and other variables. Salager states that an increase in surfactant concentration is also associated with a decrease in drop size in most cases because of an improved coalescence inhibition. Salager at 114-115.

24. <u>Singh</u>

Singh is a chapter from a textbook that was published in 2007 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Singh are Shailesh K. Singh and Venkatesh Naini.

Singh teaches the use of a microfluidizer (which is a high-pressure homogenizer) for the purpose of manufacturing emulsions with small droplet sizes. Singh discloses that microfluidizers can operate at a process pressure of up to 40,000 psi. Singh at 1999. Singh teaches that the final

droplet diameters obtained are "directly related to the process pressure used, number of passes through the microfluidizer" and "[b]ecause of their efficient droplet size reduction and ease of scale-up, microfluidizers are frequently used to prepare parenteral feeding emulsions." Singh at 1999. Furthermore, Singh illustrates the reduction in droplet size of an emulsion with an increasing number of passes through a microfluidizer [in Figure 7]. Figure 7 further shows that the droplet size continued to decrease at least until the fourth pass. *Id.* at 2000.

25. <u>Sjögren</u>

Sjögren is a journal article that was published in 2013 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Sjögren are Erik Sjögren, Jan Westergren, Iain Grant, Gunilla Hanisch, Lennart Lindfors, Hans Lennernäs, Bertil Abrahamsson, and Christer Tannergren.

Sjögren evaluates the predictive performance of the mechanistic physiologically based absorption model GI-SIM in estimating the *in vivo* performance of Two New different orally administered drug formulations, including aprepitant. Sjögren at Abstract, 685. Sjögren discloses that aprepitant is highly lipophilic (having a $\log D_{7.4} = 6.9$) and poorly soluble. *Id.* Sjögren reports aprepitant as an ampholyte compound with a weak basic ($pKa = 2.4$) and weak acidic group ($pKa = 9.4$), indicating the molecule remains largely uncharged at around neutral pH. Sjögren also reports that aprepitant exhibits "significant partitioning into micelles" and its solubility in biorelevant media, such as FaSSIF (Fasted State Simulated Intestinal Fluid, which contains bile salt and lecithin), is considerably higher compared to buffer. *Id.*

26. <u>Tsagogiorgas</u>

Tsagogiorgas is a journal article that was published in 2013 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors

of Tsagogiorgas are Charalambos Tsagogiorgas, Sonja Theisinger, Per Holm, Manfred Thiel, Michael Quintel, and René Holm.

Tsagogiorgas discloses that propofol has low solubility in water and high lipophilicity; hence the compound is commercially formulated as an aqueous oil-in-water emulsion. Tsagogiorgas at 1310. The authors further mention that because of propofol's low oral bioavailability – approximately 10% in rats, 4.2–6% in mice and negligible in humans thus – it is administered intravenously for clinical purposes. *Id.*

27. <u>Washington</u>

Washington is a journal article that was published in 1996 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The author of Washington is C. Washington.

Washington describes factors influencing the stability of phospholipid-stabilized emulsions. Washington at Abstract. Washington states that emulsions can be stabilized by phospholipids, teaching that "[t]he majority of phospholipids from egg or soya lecithin, the commonest sources, are unsaturated, and these materials are widely used as emulsifiers for intravenous use." *Id.* at 133. Washington further discloses that "[t]he proper selection of pH is thus critical in this type of formulation. If the pH is too high (or low for an acidic drug), the drug will not be ionized, and will not contribute to the zeta potential." *Id.* at 141.

28. <u>Weng</u>

Weng is a journal article that was published in 2012 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Weng are Yan Weng, Cheng Pan, Jia Meng, Bin Tian, Miaomiao Xi, Zhifu Yang, Yuwen Li, Yue Guan, Xing Tang, and Aidong Wen.

Weng discusses emulsions and discloses that "[e]mulsifiers are another essential component of lipid emulsions." Weng at 1157. Further disclosing, "[t]hough various emulsifiers on the market are concerned, lecithin should always be the first choice. The natural lecithins, including egg yolk lecithin and soybean lecithin, can be totally biodegraded and metabolized, so they are regarded as well-tolerated and non-toxic compounds with excellent biocompatibility, and suitable for long-term use and high-dose infusion." *Id*. Weng further discloses that "[t]he aqueous phase [of the emulsion] should be augmented by the incorporation of ionic or osmotic agents, antioxidants, buffers, and preservatives as required." *Id.* at 1159. Weng teaches the use of sodium oleate as a co-emulsifier and a buffer, further disclosing that "SO [sodium oleate] had a certain buffering capacity to reduce the pH change to a minimum … Hence, a small amount of SO was often used in commercial parenteral emulsions …" *Id.*

29. <u>Zhou 2012</u>

Zhou 2012 is a journal article that was published in 2012 and is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exceptions under § 102(b) apply. The authors of Zhou 2012 are Zhou Wei, Chen Fei, Chen Ning, Mao Ke.

Zhou 2012 discloses aprepitant emulsion formulations for intravenous injection containing soybean oil, egg yolk phospholipid, oleic acid, and poloxamer. Zhou 2012 at Abstract. Zhou 2012 explains that injectable emulsions of aprepitant were pursued to improve the intended delivery of the drug since patients suffering from nausea and vomiting, including CINV, were prone to vomiting drugs taken orally, which led to incomplete absorption and ineffective treatment. *Id.* at 1003.

Zhou 2012 states that the type and amount of emulsifiers as well as the amount of oleic acid had a beneficial effect on the stability of the product. Based on the results to optimize the

formulation, Zhou 2012 found that egg yolk phospholipid E80 was preferable to soybean phospholipid because it did not change color after autoclaving. *Id.* at 1006.

Zhou 2012 further discloses the process for preparing the injectable emulsion. *Id.* at 1005. The process involves preparing a preliminary emulsion by mixing the components and then homogenizing the emulsion with multiple passes (up to 7) at varying pressure ranging from 300-700 bar to obtain the final emulsion with the desired droplet size. *Id.* Zhou also reports the final aprepitant emulsion was stable and showed no de-emulsifying or crystal formulation after sterilization, storage under refrigerated conditions for 3 months, or storage at ambient conditions for 3 months. *Id.* at 1006.

30. <u>Zhou</u>

Zhou is a Chinese patent publication, CN 102379845, entitled "Aprepitant microemulsion for injection and preparation method thereof." The application was published on March 21, 2012. Zhou is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1), to which no exception under § 102(b) applies.

Zhou discloses an aprepitant microemulsion for injection, containing the following components "in percentages by mass: 0.05% - 2% of aprepitant, 5% - 30% of oil for injection, 0.5% - 10% of emulsifier, 1% - 10% of co-emulsifier, 5% - 20% of protective agents, and 60% - 80% of water for injection." Zhou at [0008].[1] Zhou further discloses the use of soybean oil for the oil phase in 9.5 wt/wt % of the composition (Example 7), phospholipids (preferably egg yolk phospholipid) as the emulsifier present in around 10 wt/wt % (Examples 5 and 7), ethanol as a co-

[1] Slayback notes that in the related litigation involving Heron and Fresenius Kabi, both parties' formulation experts appear to have agreed that a POSA reading Zhou would have understood that the reference taught conventional emulsions despite the use of the term 'microemulsion' by the inventor. *See Heron Therapeutics, Inc. v. Fresenius Kabi USA, LLC et al* 1:22-cv-00985 (D.Del), Fresenius Kabi USA, LLC's Post Trial Answering Brief, D.I. 188 at 3.

emulsifier present in 3 wt/wt % (Example 5) and 5.5 wt/wt % (Example 7), and sucrose as a protective agent (Example 2), further disclosing glucose as another protective agent in 6 wt/wt % (Example 3). *Id.* at [0010], [0021], [0023], [0027], and [0032]. Zhou also discloses the pH of the "aprepitant microemulsion for injection is 6.0 – 8.0," specifically Examples 3 and 7 describe compositions where the pH was adjusted to 8. *Id.* at [0011], [0024], and [0033].

Zhou teaches the use of aprepitant injectable compositions having relatively high emulsifier/surfactant content compared to the amount of aprepitant. Examples in Zhou provide a series of injectable aprepitant microemulsions that contain emulsifier to aprepitant ratios (wt/wt %) ranging from 10:1 (Example 8), 13:1 (Example 4), 49:1 (Example 7), and 120:1 (Example 3). *Id.* at [0034], [0025], [0032], and [0023]. Additionally, Zhou discloses compositions with emulsifier to oil ratios of 2:1 and 1:1 (Examples 2 and 3, respectively). *Id.* at [0021] and [0023].

Zhou provides a method for preparing the aprepitant microemulsion for injection, by (1) mixing aprepitant and an emulsifier, adding ethanol, heating the mixture to dissolve the ingredients, stirring and adding an oil and additional ethanol, and further heating the mixture to give a clear oil phase; (2) dissolving a tonicity agent in water and heating to obtain an aqueous phase; (3) mixing the clear oil phase and the aqueous phase and stirring to form a primary emulsion, which was then added into a high-pressure homogenizer and homogenized several times at the pressure of about 1000 MPa; (4) filtering and sterilizing by passing through a 0.22 μm membrane, to obtain the aprepitant microemulsion for injection. *See* Example 2:

> Aprepitant and poloxamer were mixed and dissolved in an appropriate amount of ethanol, then heated … and stirred … was further heated to dissolve and stirred until uniform … ethyl oleate was added … and an appropriate amount of ethanol was added to dissolve … the solution was further heated … and stirred to obtain a clear oil phase; sucrose was dissolved in water for injection heated … to obtain an aqueous phase; the clear oil phase and the aqueous phase were mixed and stirred at a high speed and then mashed … the pH was adjusted to 6.8, and a

> primary emulsion was obtained; the primary emulsion was … homogenized … then filtered and sterilized with a 0.22 μm membrane, to obtain the aprepitant microemulsion for injection.

Id. at [0022].

31. <u>The '663 Publication</u>

The '663 publication, entitled "Microemulsions for use as Vehicles for Administration of Active Compounds," was published on July 12, 2001. The '663 publication is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1), to which no exception under § 102(b) applies.

The '663 publication is directed to an oil-in-water microemulsion for use as a pharmaceutically acceptable vehicle for parenteral administration of active compounds having a low solubility in water. The '663 publication at [0013]. The '663 publication further discloses that "[t]he present microemulsion comprises a polar phase containing water and optionally an agent for obtaining isotonic conditions, and one or more components (modifiers) for adjusting the polarity, a surfactant film modifier, a non-polar phase consisting of at least one pharmaceutically acceptable oil and a mixture of a hydrophilic and a hydrophobic surfactant up to 15% by weight of the total microemulsion, preferably 4-12%." *Id.* at [0016]-[0020]; *see also,* Example 1 disclosing various formulations containing a total surfactant amount >10% (wt %). *Id.* at [0030]. The '663 publication further discloses that "[p]referably the surfactant film modifier is ethanol…" and "[t]he hydrophobic surfactant is one of lecithin, sphingolipids and galacto lipids." *Id*. at [0022] and [0025].

32. <u>The '777 publication</u>

The '777 publication, entitled "Oil Emulsion for Postnatal Hormone Substitution," was published on March 29, 2007. The '777 publication is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) to which no exception under § 102(b) applies.

The ‘777 publication relates to a process for the preparation of hormone-containing oil emulsions (lipid emulsions). The ‘777 publication at [0001]. The ‘777 publication teaches that the preferred oil for use in the lipid emulsions is soybean oil. *Id.* at [0037]. The publication identifies egg lecithin as a particularly preferred emulsifier. *Id.* at [0047]. The pH of the emulsion is adjusted to around 6.0 to 9.0, preferably from 6.5 to 8.5. *Id.* at [0053]. The ‘777 publication discloses the use of sodium oleate to adjust the pH to 8.5. *Id.* at [0058].

33. <u>The ‘520 Publication</u>

The ‘520 publication, entitled “Stable Emulsion Formulations,” was published on October 25, 2007. The ‘520 publication is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1), to which no exception under § 102(b) applies.

The ‘520 publication is directed to emulsion formulations suitable for intravenous injection. The ‘520 publication discloses emulsion formulations containing an emulsifier (e.g., egg lecithin) and an oil phase (e.g., soybean oil). The ‘520 publication at [0010]-[0011]. The ‘520 publication discloses that “the formulation of the invention can further comprise at least one preservative, antioxidant, *buffering agent*, acidifying agent, alkalizing agent, antibacterial agent, antifungal agent, solubility enhancing agent, complexation enhancing agent, organic solvent, electrolyte, salt, stabilizer, *tonicity modifier*, antifoaming agent, or a combination thereof.” *Id.* at [0028] (emphasis added). The ‘520 publication discloses formulations containing a tonicity modifier in the range of 0-2.5% w/w and a charge stabilizer, such as oleate, in the range of 0-5% w/w. *Id.* Table 5 at [0180]. The ‘520 publication discloses that tris(hydroxymethyl)aminomethane (TRIS) can be used as a buffer and “the stabilizer can be *sodium oleate*, *oleic acid*, linoleic acid, stearic acid or palmitic acid.” *Id.* at [0009] and [0029] (emphasis added).

The '520 publication further discloses that the emulsions have a pH of 7 to 9.5. *Id.* at [0028]. The '520 publication teaches that "[t]he presence of sodium oleate also has an effect on the pH at which the charge on the emulsion droplets is zero. Emulsions containing sodium oleate reach neutral zeta potential at a lower pH value. These would be expected to be stable over a broader range of pH." *Id.* at [0246].

The '520 publication discloses methods of preparing emulsions, comprising "(a) mixing the aqueous phase and the charge stabilizer; (b) dissolving the irritant agent in the oil phase (c) dissolving/dispersing the emulsifier in the oil phase (d) mixing the oil phase from step (b) and the aqueous phase from step (a); (e) homogenizing the formulation; and (f) optionally adjusting pH." *Id.* at [0032]-[0038]. The '520 publication teaches that in addition to homogenizing the emulsion, fine emulsions can be created by passing the crude emulsion through a microfluidizer at a pressure greater than 20,000 psi for a minimum of 5 cycles up to a maximum of 12 cycles. *Id.* at [0197].

34. <u>The '925 Publication</u>

The '925 publication, entitled "Intravenous formulations of neurokinin-1 antagonists," was filed as U.S. Patent Application No. 12/855,889 on August 13, 2010, and was published on February 17, 2011. The '925 publication is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1), to which no exception under § 102(b) applies.

The '925 publication discloses emulsion formulations of a NK-1 receptor antagonist for intravenous administration. The '925 publication discloses that "NK-1 receptor antagonists have been shown to be useful therapeutic agents, for example, in the treatment of pain, inflammation, migraine, *nausea*, *emesis (vomiting)*, and nociception." The '925 publication at [0004] (emphasis added). The '925 publication further discloses that the present invention can be used "prior to a chemotherapy or radiation cycle or once prior or post surgery to treat CINV (Chemotherapy

Induced Nausea and Vomiting), PONV (Post Operative Nausea and Vomiting) or RINV (Radiation Induced Nausea and Vomiting)." *Id.* at [0174].

The '925 publication explores various emulsion formulations and discloses formulations where the active ingredient, aprepitant, comprises 0.4 – 1.5% of the composition. *Id.* Table 15 at [0339]. The '925 publication further discloses that "[i]n the present formulation, lecithin is the preferred emulsifier. Purified egg lecithin is the most preferred. Additional stabilizers can be added including, for example, oleic acid or sodium oleate … long chain (Soybean oil) triglycerides may also be added … Glycerin may be used as a tonicity adjustor and ethanol may be used as a co-solvent/solubilizer for the lecithin and drug…" *Id.* at [0338]. The '925 publication discloses that "[t]he preferred emulsion formulation which avoid any hemolytic effects upon bolus or slow infusion administration have an oil content of about 10% or less." *Id.* at [0017]. The '925 publication further discloses that emulsion formulations that were formulated with 20% w/w of oil were found to have a high incidence of hemolysis. *Id.* Table 17 at [0356]; *id.* at [0357] ("Reducing the oil load from 20% to 10% in the formulation produced clean hemolysis results in both the bolus route and in the slow infusion route (Table 18).") Furthermore, the emulsion formulations disclose the use of a buffer, where a buffer is present in the composition in an "amount of from 0.01% to 0.5% by weight … of the total composition." *Id.* at [0135] and Table 4 at [0229] providing a specific composition that contains about 0.5% buffer.

35. <u>The '501 Publication</u>

The '501 publication, entitled "Injectable Emulsion of Sedative Hypnotic Agent," was published on September 12, 2013. Thus, the '501 publication is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1), to which no exception under § 102(b) applies.

The ‘501 publication is directed to pharmaceutical formulations containing oil-in-water emulsions that are suitable for administration by injection. The ‘501 publication discloses that the emulsion can contain a water-immiscible solvent, wherein “[t]he water-immiscible solvent may be a plant or animal derived oil including, but not limited to, *soybean oil*, sunflower oil, safflower oil, castor oil, sesame oil, corn oil, coconut oil, olive oil, and any mixture thereof.” *Id.* at [0037] (emphasis added). Further disclosing that “[t]he amount of water-immiscible solvent used in the emulsions of the present invention may vary from about 0.1 wt % to about 50 wt % …In a further embodiment the amount ranges from about 5 wt % to about 10 wt %.” *Id.* at [0038].

The ‘501 publication additionally discloses that “[t]he pharmaceutical formulations also comprise an emulsifier. Useful emulsifiers include, but are not limited to, polyethoxylated ethers, esters and oils such as macrogols, and phospholipids of which lecithin is an example … In one embodiment, the emulsifier is lecithin.” *Id.* at [0039]. Further disclosing that “[t]he amount of emulsifier used in the emulsions of the present invention may vary from *about 0.001 wt % to about 15 wt %.*” *Id.* at [0041] (emphasis added).

The ‘501 publication further discloses that “[t]he pharmaceutical formulations also comprise a *tonicity modifier* to make the formulation isotonic with blood. Suitable tonicity modifiers include, but are not limited to, glycerol, sorbitol, xylitol, mannitol, dextrose, glucose, polyethylene glycol, propylene glycol, *sucrose*, inorganic salts such as sodium chloride and lactose.” *Id.* at [0042] (emphasis added). Wherein, “[t]he amount of tonicity modifier used in the emulsions of the present invention may vary from about 0.001 wt % to about 10 wt %.” *Id.* at [0043].

The ‘501 publication discloses that “[t]he pharmaceutical formulations optionally comprise a stabilizer that can alternately be considered a co-emulsifier. Stabilizers are beneficial in

promoting the physical stability of the emulsion over time, i.e. in retarding separation of the oil and aqueous phases, on storage. Useful stabilizers include, but are not limited to, fatty acids such as oleic acid and its sodium salt …" *Id.* at [0046]. The '501 publication also mentions that "[w]hen present, the amount of stabilizer used in the emulsions of the present invention may vary from about 0.001 wt % to about 5 wt %." *Id.* at [0047]. The '501 publication discloses formulations containing oleic acid in the range of 0.03 % to 0.3 % w/w. *Id.* Example 1 at [0093].

The '501 publication teaches that "[e]mulsion formulations must be physically stable" and "chemically stable". *Id.* at [0005]-[0006]. The '501 publication discloses that pH plays a significant role in the physical and chemical stability of the emulsion, disclosing that "pH should be controlled during manufacture and parenteral emulsion formulations may include a buffering agent to provide additional control. Any decrease in pH over the assigned shelf-life may be indicative of chemical degradation." *Id*. at [0006]. The '501 publication discloses that "[t]he pharmaceutical formulations are formulated to be at physiologically compatible pH, which is typically defined as the range from about 5.0 to about 9.0." *Id.* at [0045]. The '501 publication further discloses that "[t]he pharmaceutical formulations may optionally further comprise pH buffering agents such as, for example, sodium phosphate, sodium citrate, sodium bicarbonate, *TRIS* and amino acid buffers such as histidine. When present, the amount of buffering agent is from about 0.01 wt % to about 10 wt %." *Id.* at [0048]-[0049] (emphasis added).

The '501 publication discloses a method of preparing emulsions where:

> The pharmaceutical formulations of the present invention may be prepared by combining the water phase components, i.e. the emulsifier, tonicity modifying agent, water and optionally an additive and/or a buffering agent (aqueous phase). The aqueous mixture is then dispersed using a homogenizer. The active agent is combined with the water-immiscible solvent and stabilizing agent, and stirred until homogenously dispersed to produce an oil phase mixture (oil phase). The aqueous phase is combined with the oil phase, under

> homogenization, to produce a coarse emulsion premix. This premix is introduced into a homogenizer, which may be a microfluidizer … The homogeniser cycle is repeated to sufficiently reduce oil droplet size … whereafter the pH is adjusted to greater than about 7 … The pharmaceutical formulation is then passed through a filter system … The pressure used for the homogenisation may vary. The pressures may be between 6000 and 24,000 psi. The filters used to achieve sterilisation may be chosen by the skilled artisan and will have nominal pore size of 0.2 μm.

Id. at [0069]-[0071].

36. <u>The '016 Publication</u>

The '016 publication, entitled "Aprepitant injectable formulations," was published on November 28, 2013. The '016 publication is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1), to which no exception under § 102(b) applies.

The '016 publication discloses that aprepitant is available "for the prevention and control of acute and delayed chemotherapy induced nausea and vomiting." The '016 publication at [0003]. The '016 publication further discloses a stable and ready-to-use formulation of aprepitant that comprises a combination of a surfactant and a co-solvent. *Id.* at Abstract; *see also* at [0012] ("In the sterile liquid formulation of aprepitant, the primary co-solvent is a short-chain alcohol, for example ethanol, while the surfactants are nonionic surfactants…"). The '016 publication discloses that "aprepitant in the formulations presented herein has significant stability, even upon prolonged storage in liquid form." *Id.* at [0014]; *see also id.* Table 8 and 9 at [0051] (disclosing aprepitant formulations demonstrating extended stability for 1-2 months under accelerated stability conditions).

The '016 publication teaches that "[a]prepitant is practically insoluble in water" and hence "significant quantities of surfactant are required to achieve moderate concentrations of aprepitant in the water solution." *Id.* at [0005] and [0044]; *see also* Tables 2, 3, 4, and 5 at [0043], [0046], and [0047] disclosing the solubility data of aprepitant formulations with varying concentrations of

surfactant, demonstrating that the solubility is enhanced with an increasing concentration of surfactant. The '016 publication discloses that "naturally occurring surface active agents may be used and include various phospholipids, e.g. … such as for example soybean lecithin and egg yolk, etc." *Id.* at [0023]. The '016 publication further discloses a formulation (Formulation VIII) that contains an emulsifier:aprepitant ratio of 23:1 (wt/wt %). *Id.* Table 8 at [0051].

37. <u>WO '116</u>

WO '116, entitled "Clevidipine Emulsion Formulations Containing Antimicrobial Agents," was published on April 19, 2012. WO '116 is thus prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1), to which no exception under § 102(b) applies.

WO '116 is directed to a stable, pharmaceutical oil-in-water emulsion formulation for parenteral administration of clevidipine. WO '116 outlines certain advantages associated with an emulsion over traditional compositions. For example, for compounds with poor aqueous solubility, emulsions usually offer much better solubility. Additionally, oil-in-water emulsions also prevent the compound from adhering to plastic infusion sets that are to be used when administering the compound. WO '116 [0029].

WO '116 discloses a series of clevidipine injectable emulsions comprising clevidipine, soybean oil, glycerin, egg phospholipids, and sodium hydroxide. *See* Tables 1, 3, and 7 of WO '116 at 12, 15, and 19, respectively. The ratio of emulsifier to clevidipine as illustrated in these examples is 24:1.

38. <u>WO '160</u>

WO '160, entitled "Aprepitant compositions," was published on December 21, 2007. WO '160 is prior art to all Two New OB Patents under AIA 35 U.S.C. § 102(a)(1) and no exception under § 102(b) applies.

WO '160 discloses powder compositions – comprising aprepitant and a surfactant/emulsifier – with improved solubility properties. WO '160 at 3, ll. 1-12. WO '160 teaches that "[t]he term 'surfactant' is used synonymously with the terms 'emulsifier', 'surface active agent', 'wetting agent' and the like and is intended to mean an excipient which, when in contact with the aprepitant particles, provides for their improved wettability. Weight ratios of aprepitant to emulsifier may range from about 1:50 to 50:1." *Id*. at 7, ll. 18-22. WO '160 discloses the solubility of various powder aprepitant formulations in water, specifically the combinations of aprepitant and a surfactant (polysorbate 80 or gelucire) demonstrated the highest solubility. *See* Example 12, at 19, ll. 6-7 (Identifier F). WO '160 discloses that a 1:1 mix of aprepitant and polysorbate 80 demonstrated the highest aprepitant solubility among various other aprepitant formulations.

EXAMPLE 12: Solubility of powder compositions of aprepitant at 25 °C in water.

Identifier	Composition	Solubility (mg/ml)
A	Aprepitant (crystalline Form I)	0.0005
B	Aprepitant:PVP K30 (1:1 w/w) solid dispersion	0.001
C	Premix of Aprepitant and Aprepitant:PVP K30 (1:1 w/w) solid dispersion (1:6 w/w)	0.001
D	Premix of Aprepitant and Aprepitant:PVP K30 (1:1 w/w) solid dispersion (1:2 w/w)	0.001
E	Premix of Aprepitant and Aprepitant:PVP K30 (1:1 w/w) solid dispersion (3:2 w/w)	0.001
F	Aprepitant:Polysorbate 80 (1:1 w/w)	0.066
G	Aprepitant:Gelucire 50/16 (1:1 w/w)	0.063
H	Aprepitant:beta-Cyclodextrin (1:1 molar ratio)	0.001

VI. CLAIMS 1, 5, 9, 11, 15, 19-20, 22, 24, 26-27, AND 29 OF THE '254 PATENT ARE INVALID FOR ANTICIPATION

A claim is invalid as anticipated if every limitation in a claim is found in a single prior art reference, either explicitly or inherently. *Impax Laboratories Inc. v. Aventis Pharmaceuticals Inc.*, 468 F.3d 1366, 1381 (Fed. Cir. 2006). Zhou was published on March 21, 2012, *i.e.*, more than 1 year prior to the effective filing date of the '254 patent and is thus prior art under 35 U.S.C. § 102(a)(1), to which no exception under § 102(b) applies.

A. Claims 1, 22, and 27 of the '254 Patent are Invalid for Anticipation

Claim 1 of the '254 patent is directed to "[an] injectable pharmaceutical emulsion, comprising: about 0.7-0.8 wt % aprepitant; an emulsifier; an oil; a co-surfactant; and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %)." Independent claims 22 and 27 of the '254 patents recite identical limitations as claim 1, except they narrow the ratio of the emulsifier to aprepitant, respectively, to 23:1 (wt/wt %) and 24:1 (wt/wt %).

As mentioned above, Zhou discloses water and oil based aprepitant emulsions for injection. Zhou at [0001]. Zhou states that the aprepitant emulsions contain: 0.05 to 2 wt.% aprepitant (preferably 1.0 to 1.5 wt.%). Zhou at [0008]-[0009]. Examples 1 and 8 of Zhou disclose aprepitant emulsions containing 0.5 % and 1% (wt.) of aprepitant. Zhou also discloses the use of a co-emulsifier or co-surfactant. *Id.* at [0010]. The composition of Example 5 was reported to contain 3 wt/wt % ethanol as co-surfactant. *Id.* at [0027].

Example 4 of Zhou describes an injectable aprepitant emulsion containing 0.5 g of aprepitant and 6.5 g of egg yolk phospholipid. This would result in an emulsifier to aprepitant ratio of 13:1 (wt/wt %). Zhou at [0025]. Likewise, the ratios of the emulsifier to aprepitant reported by Examples 3 and 7 are 120:1 and 49:1 (wt/wt %), respectively. *Id.* at [0023] and [0032].

Accordingly, the emulsifier to aprepitant ratios (20:1–25:1, 23:1, 24:1) recited by the independent claims of the '254 patent fall squarely within the emulsifier to aprepitant ratios (which is, 13:1 to 120:1) disclosed in Zhou. Additionally, there is nothing in the specification of the Two New OB Patents demonstrating criticality of the entire claimed ranges of the emulsifier to aprepitant ratios. Every example in the specification is limited only to an emulsifier to aprepitant ratio of 20:1. *See ClearValue Inc. v. Pearl River Polymers Inc.,* 668 F.3d 1340, 1345 (Fed. Cir. 2012) (holding anticipation for claims directed to a process of clarifying water with alkalinity below 50 ppm in view of the prior art teaching the same process for systems with alkalinity of 150 ppm or less since "there is no allegation of criticality or any evidence demonstrating any difference across the range").

Accordingly, Zhou expressly discloses every single ingredient and the ranges of the same recited by claims 1, 22, and 27 of the '254 patent and hence for at least these reasons, anticipates those claims. *See UCB, Inc. v. Actavis Labs. UT, Inc.,* 65 F.4th 679, 687 (Fed. Cir. 2023) ("If the prior art discloses a point within the claimed range, the prior art anticipates the claim").

B. <u>Claim 9 of the '254 Patent is Invalid for Anticipation</u>

Claim 9 of the '254 patent depends on claim 8. Claim 8 depends directly on independent claim 1 and limits the oil to a series of oils, including soybean oil. Dependent claim 9 limits the quantity of oil to 9-10 wt/wt %.

Example 7 of Zhou show aprepitant compositions with 9.5% of soybean oil. *Id.* at [0032]. Thus, claim 9 of the '254 patent is invalid for anticipation.

C. <u>Claims 15 and 20 of the '254 Patent are Invalid for Anticipation</u>

Claims 13 and 20 of the '254 patent depend directly on independent claim 1. Claim 14 of the '254 patent depends on claim 13 and claim 15 in turn depends on claim 14.

Claim 13 of the '254 patent requires the composition to further comprise an osmotic agent; claim 14 limits the osmotic agent to a group of specific agents including sucrose; claim 15 further limits concentration of the osmotic agent to 3-8 wt/wt %. Claim 20 requires the composition of claim 1 to comprise sucrose.

The specification of Zhou states that the injectable aprepitant emulsion can contain 5%-20% of a protective agent and discloses sucrose as a protective agent. *Id.* at [0008] and [0010]. Therefore, Zhou anticipates claims 15 and 20 of the '254 patent.

D. <u>Claims 11, 19, and 26 of the '254 Patent are Invalid for Anticipation</u>

Claims 10 and 19 of the '254 patent depend directly on independent claim 1, claim 11 depends directly on claim 10, and claim 26 depends directly on independent claim 22.

These dependent claims are generally directed to the presence of an alcohol in the claimed emulsion, specifically ethanol for some claims, as a co-surfactant. The alcohol/ethanol is present in the composition at less than 10% wt/wt. The compositions of Example 5 and 7 of Zhou contained 3 wt/wt % and 5.5 wt/wt % ethanol, respectively, as a co-surfactant. *Id.* at [0027] and [0032]. Hence claims 11, 19, and 26 of the '254 patent are anticipated by Zhou.

E. <u>Claims 5, 24, and 29 of the '254 Patent are Invalid for Anticipation</u>

Claims 5, 24, and 29 of the '254 patent depend directly or indirectly on various independent claims which have already been discussed above. *See supra*, the discussion in section VI. A. These dependent claims limit the nature of the emulsifier to an egg lecithin or an egg phospholipid or a soy phospholipid.

Zhou disclosed that the emulsifier can be a phospholipid, including egg yolk phospholipid. *Id.* at [0010] and [0019]. Therefore, Zhou anticipates claims 5, 24, and 29 of the '254 patent.

Accordingly, for at least the reasons stated above claims 1, 5, 9, 11, 15, 19-20, 22, 24, 26-27, and 29 of the '254 patent are invalid for anticipation over Zhou. The fact that Zhou does not

recite specific descriptive examples of compositions containing every enumerated amounts (described in the specification) of each of the ingredients does not negate a finding of anticipation. *See Arthrocare Corp. v. Smith & Nephew, Inc.*, 406 F.3d 1365, 1371-1372 (Fed. Cir. 2005) ("there is no requirement that an anticipating reference provide specific examples, rather, the reference need only be enabling and describe applicant's claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention"); *see also In re Gleave*, 560 F.3d at 1334 ("As long as the reference discloses all of the claim limitations and enables the subject matter that falls within the scope of the claims at issue, the reference anticipates--no actual creation or reduction to practice is required.") (citations and quotation marks omitted).

VII. ASSERTED CLAIMS OF THE TWO NEW OB PATENTS ARE INVALID AS OBVIOUS

A. Scope and Content of the Prior Art

1. Aprepitant was known to have a very poor aqueous solubility

Aprepitant was known to have a very low solubility in water and even in some common organic solvents. *See* Emend label at 12 ("Aprepitant ... is practically insoluble in water. Aprepitant is sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile"). *Also*, the '016 publication at [0005] ("pharmaceutically relevant concentrations are typically only achieved at unacceptably high ethanol concentrations"). The compound was also reported to have a mean absolute bioavailability of "only about 60 to 65%." *Id.* at [0006]; Emend label at 13.

2. The development of emulsion formulation was known to be a promising strategy for the delivery of poorly soluble drugs

The prior art reported that for compounds with poor aqueous solubility, emulsions can offer much better solubility, and stability than conventional aqueous solutions. WO '116 at [0029];

Hippalgaonkar at 1526 (disclosing that injectable lipid emulsions have started evolving as a feasible vehicle for the delivery of promising hydrophobic drug candidates that were discarded from further development because of their low aqueous solubility). For example, propofol was reported to have an oral bioavailability of "approximately 10% in rats, 4.2–6% in mice and negligible in humans." Tsagogiorgas at 1310. In order to circumvent the poor oral bioavailability issue arising out of the high lipophilicity and low solubility of the compound in water, propofol is formulated as an oil-in-water emulsion using Intralipid® (soybean oil, egg yolk lecithin, and glycerol) and the emulsion formulation demonstrated distinct clinical advantages in pre-clinical studies. *Id.*; Baker at 862. Likewise, clevidipine – a calcium channel blocker – was reportedly characterized by low aqueous solubility in water. WO '116 at [0003]. An oil-in-water emulsion of the compound resulted in "better solubility and/or less side effects" as compared to other conventional solution formulations. *Id.*

3. Emulsifiers/surfactants were known to increase the solubility of poorly soluble drugs including aprepitant

A common challenge in the development of parenteral formulations is dealing with the solubilization of a poorly soluble active ingredient. Ching-Chiang Su at 135. The use of surfactants has been well-established in dealing with drugs having low solubility. *Id.* at 148 ("If a drug is not solubilized by aqueous pH-modification, cosolvents, complexation, or combinations of these, surfactants are often used"); Marti-Mestres at 2 ("In the Pharmaceutical field surfactants are used especially as emulsifiers, solubilizers, and wetting agents").

The '016 publication discloses a stable, ready-to-use, injectable formulation of aprepitant comprising a combination of a surfactant and a co-solvent.[2] The '016 publication at Abstract and

[2] The terms surfactant, emulsifier or emulsifying agent are often used interchangeably in the literature and refer to the same set of functional excipients. *See e.g.,* Mahato at 262 ("Emulsifying

[0002]. The solubility data of aprepitant provided in the '016 publication, with varying nature and concentrations of surfactants employed, demonstrates that the solubility of aprepitant is enhanced with increasing concentration of surfactant. For example, Tables 2 and 3 of the '016 publication disclose the solubility of aprepitant with varying concentrations of different emulsifiers/surfactants and using water alone as a solvent. *Id.* at [0043] and [0046]

TABLE 2

Surfactant	Concentration (% w/v)	Aprepitant Conc. (mg/mL)
Cremophor RH 40	10	1.24
	30	3.51
Cremophor RH 60	10	1.24
Poloxamer 188	10	ND
	30	1.24
Polysorbate 80	10	1.85
	30	4.42

TABLE 3

Polysorbate 80 Conc. (mg/mL)	Aprepitant Conc. (mg/mL)
11	0.179
22	0.308
44	0.505

As seen in the tables below, the same trend is observed – with regard to the solubility of aprepitant – with increasing surfactant content when water and ethanol are both used as a solvent mixture. *See* the '016 publication at Table 4 and Table 5 at [0047]:

TABLE 4

agents can be surfactants, hydrophilic colloids, or finely divided solid particles."); Billany at 347 (dividing emulsifying agents or emulsifiers under categories of anionic surfactants, cationic surfactants, non-ionic surfactants, and amphoteric surfactants and listing lecithin as an amphoteric surfactant).

Polysorbate 80 Conc. (mg/mL)	Aprepitant Conc. (mg/mL)
–	0.0232
11	0.560
44	0.793

TABLE 5

Polysorbate 80 Conc. (mg/mL)	Aprepitant Conc. (mg/mL)
–	3.3
11	1.936
22	3.309
44	4.182

Likewise, WO '160 discloses compositions – comprising aprepitant and a surfactant/emulsifier – with improved solubility properties. WO '160, at 3, ll. 1-12. The publication explains, "[t]he term 'surfactant' is used synonymously with the terms 'emulsifier', 'surface active agent', 'wetting agent.' and the like and is intended to mean an excipient which, when in contact with the aprepitant particles, provides for their improved wettability." *Id.* at 7, ll. 18-21. WO '160 contemplates a wide weight ratio of aprepitant to emulsifier ranging from about 1:50 to 50:1. *Id.* at 7, ll. 21-22.

Example 12 of WO '160 lists the solubility of various aprepitant formulations where only the combinations of aprepitant and a surfactant (polysorbate 80 or gelucire) demonstrated the highest solubility. *See* Example 12, at 19, ll. 6-7 (Identifiers F and G):

EXAMPLE 12: Solubility of powder compositions of aprepitant at 25 °C in water.

Identifier	Composition	Solubility (mg/ml)
A	Aprepitant (crystalline Form I)	0.0005
B	Aprepitant:PVP K30 (1:1 w/w) solid dispersion	0.001
C	Premix of Aprepitant and Aprepitant:PVP K30 (1:1 w/w) solid dispersion (1:6 w/w)	0.001
D	Premix of Aprepitant and Aprepitant:PVP K30 (1:1 w/w) solid dispersion (1:2 w/w)	0.001
E	Premix of Aprepitant and Aprepitant:PVP K30 (1:1 w/w) solid dispersion (3:2 w/w)	0.001
F	Aprepitant:Polysorbate 80 (1:1 w/w)	0.066
G	Aprepitant:Gelucire 50/16 (1:1 w/w)	0.063
H	Aprepitant:beta-Cyclodextrin (1:1 molar ratio)	0.001

Therefore, the prior art taught the utility of emulsifiers in increasing the solubility of poorly soluble drugs – including aprepitant – with increasing emulsifier content.

4. Stable injectable aprepitant emulsion having a high emulsifier content and emulsifier to aprepitant ratio were known

Zhou discloses an aprepitant microemulsion for injection, containing the following components "in percentages by mass: 0.05% - 2% of aprepitant, 5% - 30% of oil for injection, 0.5% - 10% of emulsifier, 1% - 10% of coemulsifier, 5%- 20% of protective agent, and 60% - 80% of water for injection." Zhou at [0008]. Zhou identifies phospholipids (preferably egg yolk phospholipid) as the emulsifier for the said composition. *Id.* at [0010]. Specifically, Zhou provides a series of injectable aprepitant emulsions that contain high emulsifier to aprepitant ratios. *See e.g.*, Example 8 at [0034] (disclosing an emulsifier to aprepitant ratio of **10:1**); Example 4 at [0025] (disclosing an emulsifier to aprepitant ratio of **13:1**); Example 7 at [0032] (disclosing an emulsifier to aprepitant ratio of **49:1**).

Zhou states that microemulsions are "thermodynamically stable isotropic solution" and they are useful because "the solubilities of water-insoluble drugs and lipophilic drugs can be increased with the microemulsion formulations, the absorption of macromolecular drugs in the body may be promoted and the bioavailability may be improved." *Id.* at [0005].

Also, the '016 publication discloses a stable and ready-to-use formulation of aprepitant that comprises a combination of a surfactant and a co-solvent. The '016 publication at Abstract. The '016 publication recognizes that "[a]prepitant is practically insoluble in water" and hence "significant quantities of surfactant are required to achieve moderate concentrations of aprepitant in the water solution." *Id.* at [0005] and [0044]. Table 8 of the '016 publication discloses a formulation (Formulation VIII) that contains 130 mg aprepitant in admixture with 3 g Polysorbate 80. The emulsifier: aprepitant ratio in Formulation VIII would thus be **23:1**. Furthermore, the '016 publication states "aprepitant in the formulations presented herein has significant stability, even upon prolonged storage in liquid form." *Id.* at [0014]; *see also id*. at Tables 8 and 9 at [0051] (disclosing aprepitant formulations demonstrating extended stability for 1-2 months under accelerated stability conditions).

Accordingly, both Zhou and the '016 Publication teach the use of aprepitant injectable compositions having relatively high emulsifier/surfactant content compared to the amount of aprepitant.

5. <u>Emulsifier/surfactant and its concentration were known to be critical parameters for the stability of an emulsion</u>

It was known in the literature that an emulsifier directly or indirectly improves the stability of an emulsion formulation by "reducing interfacial tension, preventing coalescence ... imparting electrical potential on the droplets ... and/or increasing viscosity." Cannon at 216. *See also,* Rossi

at 110 ("The *purpose* of *surfactants* is to emulsify the oil phase and *provide physical stability* against flocculation and coalescence during storage, which may be for extended periods of time. Surfactants provide physical stability by reducing the oil–water interfacial tension and promoting droplet–droplet repulsion."); Hippalgaonkar at 1529 ("Emulsifiers *stabilize* emulsions by *reducing the interfacial tension* of the system and by providing enough surface charge for droplet–droplet repulsion."); *also*, at 1532 ("Zeta potential ... is a useful parameter for stability assessment [of emulsions]. A number of factors such as pH, ionic strength, *type and concentration of emulsifiers* and presence of electrolytes can *affect the zeta potential* of the system.") (emphases added).

Additionally, the prior art taught that optimizing emulsifier concentration would be necessary to obtain the desired stability and pharmacological properties of an emulsion. *See e.g.,* Khan at 2719 ("The *amount* of *emulsifying* agent is one of the *most important* factors having an influence on the emulsion *stability*. Emulsifier *concentration* has a *great* impact on emulsion stability. A *concentration window existed*, out of which the emulsion stability is quickly declined. At low emulsifier concentration, the emulsion is unstable because of agglomeration of the oil droplets. At high emulsifier concentration emulsion instability occurs because of rapid coalescence"); *also*, Cannon at 215 ("Some of the *factors* that affect the physical stability of emulsions include the *type* and *concentration* of *surfactant* used to stabilize the emulsion, the phase volume ratio ... droplet size"); *further* at 216 ("Whereas an *inadequate concentration* of *surfactant* will do little to *prevent* coalescence, *undue increase* in its concentration often leads to *problems* like increased drug instability and difficulty in administration") (emphases added).

6. <u>Injectable compositions containing a high emulsifier concentration and/or a high emulsifier to drug ratio were known</u>

Cleviprex label states that clevidipine is "practically insoluble in water and is formulated in an oil-in-water emulsion." The composition contains, *inter alia*, 0.5 mg/mL of clevidipine and

12 mg/mL egg yolk phospholipids – signifying a clevidipine to emulsifier ratio of 1:24. Cleviprex label, Description. In addition, WO '116 discloses a series of clevidipine injectable emulsions comprising an identical ratio of the drug to emulsifier. WO '116, Tables 1, 3 and 7.

Likewise, Broadhead states that the use of surfactants is one of the strategies for developing parenteral formulations of drugs with low solubility. Broadhead at 331. The authors state that there are a few i.v. products that contain significant levels of surfactant, *e.g.*, Cordarone i.v. and Etoposide i.v., which contain 10% and 8%, respectively, of polysorbate (Tween) 80. *Id.* Additionally, Aquasol A (vitamin A palmitate as retinol) which is used for intramuscular administration, is reported to contain polysorbate 80 at a level of 12%. *Id.*

7. <u>Certain emulsion types were known to require a relatively high concentration of emulsifier</u>

Microemulsions are a type of system that were known to offer various advantages, including "improved drug solubilization." Klier at 1752. The authors explained that microemulsions "often require *high surfactant levels* in order to provide sufficient interfacial coverage to completely microemulsify the required levels of ingredients, as well as to provide *sufficient formulation stability* to temperature and compositional changes to meet practical storage and use requirements." *Id.* at 1752; *also,* Ching-Chiang Su at 150 ("Because of the numerous small droplets, the surface area to volume ratio of microemulsions are very high and it forms easily because of the low surface tension, typically due to *high levels of surface active species*") (emphases added). Likewise, Brime refers to Amphotericin B as "practically insoluble in water" and reports microemulsions of Amphotericin B containing 15-20% of Brij® 96V as the emulsifier. Brime at 1178 and Table 1 at 1182. Additionally, Eastoe stated that "[m]icroemulsions may be considered as a subset of emulsions, exhibiting certain unique properties." Eastoe at 688.

8. **Additional formulation limitations regarding the pH, and nature of other excipients – oil, co-surfactant, tonicity adjuster, pH modifier – were known**

Zhou discloses the use of soybean oil for the oil phase, phospholipids (preferably egg yolk phospholipid) as the emulsifier, ethanol as a co-emulsifier, and sucrose as a protective agent. Zhou at [0010]. The publication further specifies that the pH of the "aprepitant microemulsion for injection is 6.0-8.0." *Id.* at [0011]. Examples, 1-8 of Zhou outline a series of aprepitant emulsion compositions for injection that were prepared using one or more of the excipients described above. *Id.* at [0019] - [0036]. Likewise, Collins-Gold reports that "[w]hile a wide variety of surfactants are available for industrial manufacturing of foods, cosmetics, insecticides, paints, detergents and so forth, relatively few are approved *for i.v. administration*. Natural phosphatides, principally from *egg yolk* or *soybean*, are in *most widespread use*" (emphasis added). Collins-Gold at 192.

The '016 publication – which described a number of injectable aprepitant compositions – discloses that the pH of the emulsions described therein "can be adjusted to the desired pH range in order to maintain chemical stability of the drug, preferably in the range of 3 to 8 pH units." *Id.* at [0032]. The '520 publication discloses that the emulsions have a pH of 7 to 9.5. *Id.* at [0028]. Cleviprex (clevidipine injectable emulsion) has a pH of 6.0–8.0. Cleviprex label at Description.

Rossi discloses emulsions for intravenous administration must be biocompatible, biodegradable, nontoxic, sterile, isotonic, physically and chemically stable, and nonimmunogenic. Rossi at 108. Achieving "isotonicity of an injectable emulsion is important in order to avoid disturbing the state of cells in contact with the formulation." *Id.* at 112. Likewise, the '501 publication explains that the injectable emulsions reported therein "also comprise a tonicity modifier to make the formulation isotonic with blood." The '501 publication at [0042]. *Also*, *id.* at [0024] (stating that suitable tonicity modifiers include sucrose) and at [0025] (The amount of

tonicity modifier used in the emulsions may vary from about 0.001 wt% to about 10 wt %.). Zhou states that the aprepitant emulsion formulations disclosed therein preferably contain 8% - 13% of a protective agent. Zhou at [0009]. Sucrose is mentioned as one of the alternatives. *Id.* at [0010], Example 2 at [0021]. Additionally, a number of examples mention the use of 5 or 8% glycerol, a well-known tonicity modifier. *Id.* at Example 1 at [0019]; Example 4 at [0025]; Example 5 at [0027].

Weng reports that sodium oleate can function as a co-emulsifier and a buffer in an emulsion system. Weng at 1159 (sodium oleate "had a certain buffering capacity to reduce the pH change to a minimum"). *Also*, the '520 publication teaches that "[t]he presence of sodium oleate also has an effect on the pH at which the charge on the emulsion droplets is zero. Emulsions containing sodium oleate reach neutral zeta potential at a lower pH value. These would be expected to be stable over a broader range of pH." *Id.* at [0246]. The '925 publication discloses an emulsion formulation of a NK-1 receptor antagonist where a buffer is present in the composition in an "amount of from 0.01% to 0.5% by weight ... of the total composition." The '925 publication at [0135] and Table 4 at [0229] providing a specific composition that contains about 0.5% buffer.

B. <u>Level of Ordinary Skill in the Art</u>

The subject matter covered by the Asserted Claims of the Two New OB Patents generally involves an injectable aprepitant emulsion composition comprising excipients such as, an emulsifier, an oil, a pH modifier, a co-emulsifier, and water. For purposes of these Invalidity Contentions, Defendants have assumed that a POSA pertaining to the subject matter described by the Asserted Claims of the Two New OB Patents would be a person with an advanced degree in pharmaceutical science and several years of experience (*e.g.*, a Master's degree scientist with 4-6 years of experience, or a Ph.D. trained scientist with 2-4 years of experience) in pharmaceutical formulation development of injectable formulations, including emulsions and those for

intravenous use. Such a person would be working together in a multidisciplinary team with other formulation development personnel (analytical chemist, manufacturing science etc.), pharmacologists, practicing physicians and/or clinicians having experience with dosing and administration of injectable drugs for the prevention of nausea and vomiting, including CINV and PONV.

C. Differences Between the Prior Art and the Asserted Claims of the Two New OB Patents

The subject matter covered by the Two New OB Patents relate to an injectable emulsion composition of the drug aprepitant, which was well-known in the art for the prevention of nausea and vomiting, including CINV and PONV. *See e.g.*, Emend label at 1 (INDICATIONS AND USAGE), Zhou at [0003]; the '016 publication at [0003]. Aprepitant was originally approved by the FDA as an oral dosage form. Hargreaves at 41; the '016 publication at [0003]. Subsequently a nanoparticulate oral composition of aprepitant as well as a water-soluble form of aprepitant (a prodrug known as fosaprepitant that converts to aprepitant *in vivo*) were developed. Hargreaves at 44, 46; the '016 publication at [0006] and [0008]-[0009].

Drawbacks of these commercial formulations were well-established before the effective filing dates of the Two New OB Patents. For example, the '016 publication states that "the bioavailability of the compound when given orally is *only* about 60-65%." The '016 publication at [0006] (emphasis added). Additionally, the prior art taught the undesirability and inconvenience of administering a drug orally to patients that are susceptible to nausea and vomiting. Patients taking oral aprepitant may experience reduced drug absorption and ineffectiveness due to vomiting. Zhou at [0006]. Accordingly, the availability of both an oral and an intravenous formulation of aprepitant was suggested to increase the delivery options available to oncologists and patients and provide maximum clinical dosing flexibility. Hargreaves at 44. Further, with

respect to fosaprepitant, the additional steps required to synthesize the prodrug added "significant complexity and cost to the drug." The '016 publication at [0008]; *see also* Zhou at [0006] ("Although currently the prodrug of aprepitant, fosaprepitant dimeglumine injection has been developed, it was synthesized through complex reactions on the basis of aprepitant and the cost is higher, which greatly increases the burden on patients").

Accordingly, POSA would have been motivated to explore and prepare an alternative injectable composition of aprepitant. It was known in the art that highly hydrophobic drugs, *i.e.*, those with high logP values, are usually poorly soluble in water. Formulating such drugs as an emulsion allows its administration with increased bioavailability than what can be achieved via traditional routes. Mahato at 255. *See also*, Zhou at [0005] ("As the solubilities of water-insoluble drugs and lipophilic drugs can be increased with the microemulsion formulations, the absorption of macromolecular drugs in the body may be promoted and the bioavailability may be improved. The drugs can be protected from enzymatic degradation in the gastrointestinal tract to some extent, and the stability of unstable drugs may be enhanced"). Consequently, as aprepitant was known to be highly insoluble in water, a number of prior art references disclosing parenteral formulations of aprepitant have focused on developing emulsion-based formulations to ensure solubility of the drug. *See generally* Zhou and the '016 publication.

Zhou expressly discloses every single claimed ingredient of the Asserted Claims of the Two New OB Patents in amounts that overlap with or are very close to the ranges recited by these claims. For example, Zhou states that the aprepitant emulsions reported therein contain: 0.05 to 2 % (wt.) aprepitant; 5 to 30 % (wt.) oil; 0.5 to 10 % (wt.) emulsifier; 1 to 10 % (wt.) co-emulsifier; 5 to 20 % (wt.) of protective agent (which is tonicity modifier); and 60 to 80 % (wt.) water for injection. Zhou at [0008]. Zhou further discloses that the oil can be <u>soybean oil</u>, the emulsifier is

preferably egg yolk phospholipid, the co-emulsifier is preferably ethanol, and the protective agent (tonicity modifier or osmotic agent) can be sucrose. *Id.* at [0010]. Further, the emulsifier proportions (wt.%) and emulsifier to aprepitant ratios (wt./wt.%) disclosed in various examples of Zhou are either very close or encompass the emulsifier content and the said ratios recited by the Asserted Claims of the Two New OB Patents. *See e.g.*, Examples 2, 5 and 8 at [0021], [0027], and [0034] respectively, (all reporting compositions with an emulsifier content of 10%); Example 8 at [0034] (disclosing an emulsifier to aprepitant ratio of 10:1); Example 4 at [0025] (disclosing an emulsifier to aprepitant ratio of 13:1); Example 7 at [0032] (disclosing an emulsifier proportion of 9.8% and an emulsifier to aprepitant ratio of 49:1); Example 3 at [0023] (disclosing an emulsifier to aprepitant ratio of 120:1). Zhou states that a microemulsion is a "thermodynamically stable isotropic solution." *Id.* at [0005].

Accordingly, the supposed inventive formulations described by the Asserted Claims of the Two New OB Patents are nearly identical to the compositions described by Zhou – except for a slight variation in the amount of emulsifier (0.5 to 10 wt.% in Zhou as compared to various percentages between 13-20 wt.% by the Asserted Claims of the Two New OB Patents) – a fact that was not contested by the Applicants during the prosecution of the Two New OB Patents. However, for the reasons outlined below, a POSA would have been motivated to test the emulsions of Zhou to determine their stability and increase the known quantity of emulsifier if any crystallization of aprepitant was observed (because poor solubility of the drug, as well as improvement in solubility with increasing emulsifier concentration was taught in the prior art) to ensure aprepitant remained solubilized and the emulsion is stable. Also, at least for the reasons stated below, a POSA would have had a reasonable expectation of success in doing so.

1. Claims 1, 22, and 27 of the '254 patent, and claims 1 and 30 of the '255 patent are invalid as obvious

Claim 1 of the '254 patent is directed to "[an] injectable pharmaceutical emulsion, comprising: about 0.7-0.8 wt % aprepitant; an emulsifier; an oil; a co-surfactant; and water, wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %)." Independent claims 22 and 27 of the '254 patents recite identical limitations as claim 1, except they narrow the ratio of the emulsifier to aprepitant, respectively, to 23:1 (wt/wt %) and 24:1 (wt/wt %).

Claim 1 of the '255 patent recites an injectable emulsion, comprising 0.7-0.8 wt % aprepitant; 13 wt/wt % to 20 wt/wt % of an emulsifier; an oil; a co-emulsifier which is an alcohol; a tonicity modifier; a pH modifier; and water; wherein the pH of the emulsion ranges from about 7.5 to 9.0. Independent claim 30 is directed to an injectable pharmaceutical emulsion, comprising about 0.7-0.8 wt % aprepitant; an egg phospholipid emulsifier; an oil; a co-surfactant; water; and a pH modifier, wherein the ratio of the emulsifier to aprepitant is about 20:1 to 25:1 (wt/wt %).

a) Use of aprepitant for the treatment of emesis

The use of aprepitant for the treatment of nausea and vomiting was known. The Emend label at 1; the '016 publication at [0003] (aprepitant is available for the "prevention and control of acute and delayed chemotherapy induced nausea and vomiting and for prevention of postoperative nausea and vomiting").

b) Injectable pharmaceutical emulsion with 0.7-.08 wt.% aprepitant

Both Zhou and the '016 publication disclose emulsions of aprepitant for injection. Zhou at [0001]; the '016 publication at [0054] to [0056]. Zhou states that the aprepitant emulsions contain: 0.05 to 2 wt.% aprepitant (preferably 1.0 to 1.5 wt.%). Zhou at [0008]-[0009]. Examples 1 and 8 of Zhou disclose aprepitant emulsions containing 0.5 % and 1% (wt.) of aprepitant. Thus, aprepitant concentrations disclosed by Zhou overlap with the corresponding concentrations recited by the asserted independent claims of the Two New OB Patents.

c) <u>Emulsifier/egg yolk lecithin content ranging from 13-20 wt.% and emulsifier/egg yolk lecithin to aprepitant ratio ranging from about 20:1 to 25:1</u>

As an initial matter, Zhou reported aprepitant emulsions containing about 10 wt/wt % egg phospholipids. *Id.* Examples 5 and 7, at [0027] and [0032]. Furthermore, it was known in the literature that the emulsifier and its concentration are some of the most important factors that directly or indirectly affect the stability of an emulsion. *See e.g.,* Rossi at 90 ("It is *important* to state that *surfactants* provide the emulsions ... with *kinetic stability*, which delays the destabilization process ... surface-active agents can provide stability for *several years*, which is long enough for the system to be useful for practical purposes"). Additionally, the prior art explicitly taught that the "*amount of emulsifying agent* is one of *the most important factors* having an influence on the emulsion stability. Emulsifier *concentration* has a *great impact* on emulsion stability." Khan at 2719; *see also* Cannon at 215 ("Some of the factors that affect the physical *stability* of emulsions include the *type* and *concentration* of *surfactant* used to stabilize the emulsion") (emphases added).

The prior art explained that one of the mechanisms by which the emulsifier/surfactant concentration directly affects the stability of an emulsion is by controlling the droplet size and for the purpose of stability and safety of an injectable emulsion, a smaller droplet size was preferred. In particular "type and *concentration* of lipid and *emulsifier* used, can *significantly* affect the *droplet size* ... larger sized droplets (>than 250 nm compared to <100 nm) were *cleared faster* ... compared to small sized emulsion, *large* size emulsions were *rapidly eliminated* from the blood circulation ... [and] emulsions with droplet size larger than 200 nm effectively *inhibited* drug penetration into [various organs] indicating size controlled disposition in the body." Hippalgaonkar at 1537 (emphases added). *Also*, Collins-Gold at 193 "[f]or parenteral use, a droplet mean diameter of less than 1 μm is highly desirable." Since droplet size was also known

to directly impact "toxicity and stability of the emulsion system" the prior art recognized "droplet size and distribution" as some of the most important characteristics of an injectable emulsion. Hippalgaonkar at 1531.

It was further known in the literature that a decrease in "the *emulsifier concentration* ... would lead to an increase in the surface tension and an *increase* in the *droplet size*." *Id.* at 1532. Conversely, an *increase* in emulsifier *concentration* was known to cause a *reduction* in the droplet size up to an optimum concentration, beyond which it was reported to result in an increase in the viscosity of the medium. *See* Collins-Gold, Table I at 194 (increased "surfactant concentration" results in "smaller droplet size until optimum, then increased viscosity"); Klang at 64 ("an *increase* in *lecithin concentration* leads to the production of *smaller particles* due to an increased surfactant to oil volume ratio, which in turn leads to *enhanced physical stability*"); Salager at 114-115 ("It is worth noting that an *increase* in *surfactant* concentration is also associated with a *decrease* in drop size in most cases because of an *improved coalescence inhibition*") (emphases added). Thus, a POSA aiming to prepare an injectable pharmaceutical emulsion of aprepitant with reduced droplet size would have been motivated to explore optimally increasing the emulsifier concentration.

In addition to the positive effect of lowering the droplet size, a relatively high emulsifier concentration was also known to have a beneficial effect on the solubility of poorly water-soluble drugs like aprepitant. Aprepitant was known to be an ampholytic compound, *i.e.*, having both a weak basic group (p*K*a = 2.4) and weak acidic group (p*K*a = 9.4), and therefore remained largely uncharged at around neutral pH. Sjögren at 685. Aprepitant is also highly lipophilic and poorly soluble in water. *Id.* at 685. The '016 publication states that due to the poor solubility of aprepitant, bioavailability of the commercial oral formulation is only about 60-65%. The '016 publication at [0006]. The compound was also known to be substantially insoluble in oil. The '016 publication

at [0054]. Hence, a POSA, would not have expected that modifying the formulation of Zhou to increase the amount of water or soybean oil in the emulsion would improve the solubility of aprepitant in the composition and hence would have focused on increasing the emulsifier content to achieve desired solubility of the drug.

In this regard, it was reported in the prior art that aprepitant exhibits "significant partitioning into micelles" and its solubility in biorelevant media, such as FaSSIF (Fasted State Simulated Intestinal Fluid, which contains bile salt and lecithin), is considerably higher compared to buffer. Sjögren at 685. *See also*, Washington at 139 ("drugs [that] are poorly soluble in both water and oil, can only be loaded into an emulsion by *adsorbing to the droplet interface*." (emphasis added)). It follows from this disclosure that a larger number of small droplets would be needed (as opposed to fewer droplets of larger size) such that a significantly large surface area is available for the entire drug to remain loaded in the emulsion. *See e.g.*, Baker at 862 (stating that a reduction in droplet size from 1.0 μm in diameter to 0.1 μm results in approximately a 42 time increase in the oil-water surface area). As indicated earlier this would entail a higher emulsifier content. The '016 publication, Tables 2-5 at [0043], [0046] and [0047] (disclosing solubility data of aprepitant with varying concentrations of surfactant and demonstrating that the solubility is enhanced with increasing surfactant concentration); *also*, Example 12 of WO '160, Identifier F at 19 (showing that a 1:1 mix of aprepitant and polysorbate 80 (an emulsifier) demonstrated the highest aprepitant solubility among various other aprepitant formulations that did not contain an emulsifier). Increased oil-water interfacial area, via reduction in droplet size was also taught to facilitate rapid release of the drug into the blood. Baker at 862 ("The total interfacial surface area is a highly important factor in the rate of drug release from a drug containing droplet. This in turn is dependent on the size and number of oil droplets resulting from the injection"). Therefore,

teaching of the prior art would have persuaded a POSA to use an increased proportion of emulsifier if any crystallization or precipitation of the drug were observed when preparing an injectable emulsion formulation of aprepitant.

The presence of relatively high quantities of emulsifier in oil-in-water emulsions was known in the art. For example, Bagwe indicated that emulsions could contain 1-20% of emulsifier. Bagwe, Table 2 at 82. The '501 publication discloses oil-in-water emulsions suitable for injection, wherein the emulsifier (*e.g.*, lecithin including egg yolk lecithin), is present in up to 15 wt.%. The '501 publication at Abstract, [0001], [0039]-[0041]. The '663 publication at [0020] (mentioning that the emulsions disclosed therein can contain up to 15% by wt. of emulsifier). Patravale at 260 (Table 9.1 states that the surfactant content in microemulsions can vary from 1-20%). Klang also discloses emulsion systems where the surfactant/co-surfactant mixtures may be present in amounts of 20 to 50 wt.%. Klang at 57. Additionally, some commercial injectable emulsions were known to contain 10% or more emulsifier. Broadhead at 331 (mentioning Cordarone i.v. and Etoposide i.v. contain 10% and 8%, respectively, of polysorbate 80; and Aquasol A (vitamin A palmitate as retinol) contains polysorbate 80 at a level of 12%).

Furthermore, the prior art taught that because of the smaller droplet size, microemulsions usually require a relatively high emulsifier concentration for stabilization. *See* Mahato at 257 ("[Microemulsions] often contain a *high concentration of the emulsifier(s)* and a cosolvent (such as ethanol)"); Ching-Chiang Su at 150 ("Because of the numerous small droplets, the surface area to volume ratio of microemulsions are very high and it forms easily because of the low surface tension, typically due to *high levels of surface active species*"); Bagwe at 88 ("large concentration (10-40%) of surfactant is required to stabilize the newly created interface of microemulsion droplets") (emphases added). Indeed, Brime reported the preparation of injectable microemulsions

of Amphotericin B (a drug with low aqueous solubility) where the emulsifier (Brij® 96V) concentration varied from 10-20 wt. %. Brime at 1182. Furthermore, Eastoe stated that "[m]icroemulsions may be considered as a subset of emulsions." Eastoe at 688.

While higher emulsifier/surfactant concentration was generally favorable for the stability of an emulsion and also to achieve increased dissolution of drugs with poor aqueous solubility, the prior art also cautioned that an excessive emulsifier concentration would be detrimental for the emulsion composition and suggested maintaining an optimum concentration. *See e.g.,* Khan at 2719 ("A *concentration window existed*, out of which the emulsion stability is quickly declined. At low emulsifier concentration, the emulsion is unstable because of agglomeration of the oil droplets. At high emulsifier concentration emulsion instability occurs because of rapid coalescence"); *also*, Cannon at 216 ("Whereas an *inadequate concentration* of *surfactant* will do little to *prevent* coalescence, *undue increase* in its concentration often leads to *problems* like increased drug instability and difficulty in administration ... *Excess* surfactant molecules will tend to *self-associate*, forming micellar or lamellar structures, which may *compromise* the *effectiveness* of the emulsion.") (emphasis added). Accordingly, the combined teaching of the prior art would have informed a POSA that it is critical to optimize the concentration of the surfactant of an emulsion composition in order to balance the various parameters and to achieve appropriate efficacy.

In addition, lecithins were widely known as one of the most commonly employed emulsifiers which are "biocompatible and hence eliminate toxicity concerns." Bagwe at 83. *Also*, Collins-Gold at 192 ("[w]hile a wide variety of surfactants are available for industrial manufacturing of foods, cosmetics, insecticides, paints, detergents and so forth, relatively few are approved *for i.v. administration*. Natural phosphatides, principally from *egg yolk* or *soybean*, are

in *most widespread use*") (emphasis added). Weng teaches that "lecithin should always be the first choice. The natural lecithins, including egg yolk lecithin and soybean lecithin, can be totally biodegraded and metabolized, so they are regarded as well-tolerated and non-toxic compounds with excellent biocompatibility, and suitable for long-term use and high-dose infusion." Weng at 1157. Hippalgaonkar explained that since natural lecithin, obtained from egg yolk, are biocompatible, nontoxic, and are metabolized like natural fat, these emulsifiers are used extensively to stabilize injectable emulsions. Hippalgaonkar at 1529. Accordingly, because the prior art recognized lecithins as one of the very few emulsifying agents that are regarded as safe for parenteral administration, a POSA would have been assured to use a lecithin in relatively high concentration, as required to achieve emulsion stability and avoid precipitation of the drug.

It also follows that if the amount of lecithin emulsifier were to increase in an emulsion while keeping the amount of aprepitant the same, the emulsifier:aprepitant ratio would consequently increase. For instance, Example 4 of Zhou contains 0.5 wt.% aprepitant and 6.5 wt.% emulsifier, *i.e.*, with an emulsifier:aprepitant ratio of 13 to 1. Increasing the amount of lecithin to 10 wt.%, while keeping the amount of aprepitant the same, would shift the ratio of emulsifier:aprepitant to 20:1. This emulsifier:aprepitant ratio – 20:1 – overlaps with the ranges of emulsifier:aprepitant ratios recited by the Asserted Claims of the Two New OB Patents (*i.e.*, about 20:1 to 25:1). *See In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("In cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a prima facie case of obviousness.")

d) <u>An oil</u>

The asserted independent claims of the Two New OB Patents require the emulsion to contain an oil. Zhou discloses emulsions that can contain an oil. Zhou at [0008]-[0010].

e) <u>A pH modifier and a pH of 7.5 to 9.0</u>

The asserted independent claims of the '255 patent require the emulsion to contain a pH modifier. Claim 1 of the '255 patent also requires that the pH of the claimed emulsion ranges from about 7.5 to 9.0.

The '016 publication mentions the use of a pH adjusting agent in preparing an aprepitant composition. Zhou specifies that the pH of the "aprepitant microemulsion for injection is 6.0-8.0." *Id.* at [0011]. Also, Examples 3 and 7 describe specific compositions where the pH was adjusted to 8. *Id.* at [0024] and [0033]. *See In re Peterson,* 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("even a slight overlap in ranges establishes a *prima facie* case of obviousness").

In addition, it was well-established in the prior art that pH can affect the stability of an emulsion. For example, Hippalgaonkar explained that the pH of the lipid emulsions "decrease during sterilization and storage as a result of increase in free fatty acid content due to the hydrolysis of phosphatidylcholine (PC) and phosphatidylethanolamine (PE) ... A decrease in pH can lead to a decrease in the zeta potential of the emulsion droplets and ultimately lead to emulsion instability." Hippalgaonkar at 1532. Similarly, Klang discloses that the negative surface potential of lecithin-based nanoemulsions is "markedly pH-dependent" and stability can be improved by adjusting the formulation to an alkaline pH. Klang at 70. *See also*, Rossi at 112 ("The desired pH [of an injectable emulsion] is usually between 7 and 8 to maintain physiological compatibility and minimize hydrolysis of the oil and phospholipids."); Patravale at 266 ("[i]n the case of lecithin-based microemulsions, adjustment of the initial pH at 7-8 is also important in order to minimize the hydrolysis of the phospholipids and the triglycerides to fatty acids, which can decrease the pH of the microemulsion and may affect the stability."). In addition, like Zhou several prior art references provided examples of oil-in-water emulsions whose pH were adjusted within or overlapping with the claimed pH range. *See e.g.*, the '501 publication at [0045] ("formulated to

be at physiologically compatible pH ... from about 5.0 to about 9.0"); the '520 publication at [0028] (disclosing emulsions having a pH of 7 to 9.5).

f) A co-emulsifier or co-surfactant which can be an alcohol and a tonicity modifier such as sucrose

Some of the independent Asserted Claims of the Two New OB Patents recite a co-emulsifier/co-surfactant which can be an alcohol; and a tonicity modifier/ osmotic agent. Zhou discloses the use of ethanol as a co-emulsifier, and sucrose as a protective agent. Zhou at [0010]. *Also*, at 1, claim 1 ("the co-emulsifier is one or several of ethanol ..."). The composition of Example 5 of Zhou was reported to contain 3 wt/wt % ethanol as co-surfactant and 5 wt/wt % glycerin as a protective agent (*i.e.*, a tonicity modifier or an osmotic agent).

g) Claims 1, 22, and 27 of the '254 patent, and claims 1 and 30 of the '255 patent are invalid as obvious

Accordingly, as explained above, the sole limitation recited by most of the Asserted Claims of the Two New OB Patents and not explicitly disclosed in the prior art is the amount of emulsifier present in an aprepitant composition – ultimately leading to an emulsifier to aprepitant ratio ranging from about 20:1 to 25:1 (wt./wt. %) or an emulsifier concentration of about 13-20 wt. %.

However, given the teaching of Zhou (having an emulsifier content of 10 wt./wt. %) in conjunction with the prior art disclosure that – (1) aprepitant is poorly soluble in both water and oil and that the low aqueous solubility affects the bioavailability of the drug, (2) surfactants/emulsifiers are effective in enhancing the solubility of aprepitant, (3) the emulsifier concentration with an *optimum* concentration *window* was a well-known parameter affecting stability and pharmacological properties of emulsions, (4) lecithins as emulsifiers can be completely metabolized *in vivo* thereby eliminating any toxicity concern in a formulation even when used in relatively high concentrations, and (5) there existed an optimum "concentration window" for emulsifiers that imparts stability to an injectable emulsion – a POSA would have

been motivated to increase the quantity of emulsifier reported in the formulations of Zhou to improve any potential stability and drug solubility problems and thus would have arrived at an aprepitant formulation containing an amount of emulsifier falling within 13-20 wt./wt. %. *See Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 730 (Fed. Cir. 2017) ("The only elements … that were not expressly disclosed in the prior art … are … details that one of ordinary skill would have utilized via routine experimentation, armed with the principles disclosed in the prior art. Thus, it was reasonable for the district court to deduce from the evidence that the [missing elements], if not already known, would have been discovered by routine experimentation while implementing known principles."). As the Federal Circuit recently clarified, there is no "such a brightline rule" requiring routine experimentation to apply only where the claimed invention identifies the 'optimum or workable ranges' of previously disclosed conditions. *See Purdue Pharma L.P. v. Accord Healthcare, Inc*., No. 2023-1953, slip opin. at 28, (Fed. Cir. Dec. 30, 2024). Accordingly, absence of a prior art aprepitant emulsion composition having an emulsifier content that encompasses the claimed emulsifier concentration does not negate finding of obviousness under routine experimentation.

Moreover, given the close proximity of the prior art and the claimed emulsifier concentrations (10 wt./wt. % vs. 13-20 wt./wt. %) and the fully overlapping nature of the prior art emulsifier:aprepitant ratios – 10:1, 13:1, 23:1, and 49:1 – with the claimed emulsifier:aprepitant ratios (ranging between about 20:1 to 25:1), and the teaching of the prior art that a concentration window (*i.e.*, a lower and an upper limit) existed for the emulsifier concentration, a POSA would have arrived at the claimed ratios as a matter of routine experimentation. *See In re Applied Materials*, 692 F.3d 1289, 1293 (Fed. Cir. 2012) ("identification of an optimal range of a result-effective variable as being within the ordinary skill in the art") (*citing In re Aller,* 220 F.2d 454,

456 (C.C.P.A. 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.").

Also, given the prior art disclosures regarding the need to use a relatively high concentration of an emulsifying agent for microemulsions, a POSA would have had a reasonable expectation of success in preparing such an emulsion. *See In re Kubin*, 561 F.3d at 1360 ("Responding to concerns about uncertainty in the prior art influencing the purported success of the claimed combination, this court stated: [o]bviousness does *not* require *absolute predictability* of success … all that is required is a *reasonable expectation* of success" (*citing In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988))) (emphasis added).

Accordingly, independent Asserted Claims of the Two New OB Patents – claims 1, 22, and 27 of the '254 patent, and claims 1 and 30 of the '255 patent – are invalid as obvious under AIA 35 U.S.C. § 103 over the prior art discussed above.

2. <u>Claim 22 of the '255 patent is invalid as obvious</u>

Claim 22 of the '255 patent depends on independent claim 1 and limits the aprepitant content to 0.7 wt/wt %.

All of the independent Asserted Claims of the Two New OB Patents contain the identical limitation with regard to the amount of aprepitant. *See supra*, the discussion in section VII. C. 1. b. Thus, claim 22 of the '255 patent is invalid as obvious over the prior art.

3. <u>Claims 5-7, 24, and 29 of the '254 patent, and claims 5-11, and 23-29 of the '255 patent are invalid as obvious</u>

Claims 5-7, 24, and 29 of the '254 patent depend directly or indirectly on claims 1, 22, and 27, respectively. Claims 5-11 and 23-29 of the '255 patent depend directly or indirectly on claim 1.

These dependent claims recite the quantity (16 wt/wt %, 17 wt/wt %, or 18 wt/wt %) and/or the nature (phospholipid or egg lecithin) of the emulsifier present in the claimed compositions. Additionally, claims 8, 24, and 27-29 of the '255 patent specify an egg lecithin:aprepitant ratio or a phospholipid:aprepitant ratio (of about 20:1 to 25:1 (wt./wt. %), 23:1 wt./wt. %, 24:1 wt./wt. % and 25:1 wt./wt. %).

All of these limitations have been addressed above in connection with the obviousness analysis of some of the independent Asserted Claims of the Two New OB Patents. *See supra*, the discussion in section VII. C. 1. c. Hence, claims 5-7, 24, and 29 of the '254 patent, and claims 5-11, and 23-29 of the '255 patent are invalid as obvious over the prior art.

4. Claim 9 of the '254 patent, and claim 13 of the '255 patent are invalid as obvious

Claim 9 of the '254 patent depends on claim 8. Claim 8 depends directly on independent claim 1 and limits the oil to a series of oils, including soybean oil. Claim 13 of the '255 patent depends directly on claim 12, which in turn depends directly on independent claim 1.

These dependent claims – claim 9 of the '254 patent and claim 13 of the '255 patent recite the quantity (9-10 wt/wt %) and/or the nature of the oil (a group of oils, including soybean oil) present in the claimed compositions. Zhou discloses emulsions containing 5 to 30 wt.% oil, preferably 7 to 15 wt.%. Zhou at [0008]-[0009]. Zhou further discloses the oil can be soybean oil. *Id.* at [0010]. Examples 7 and 8 of Zhou show aprepitant compositions with 9.5% of soybean oil and 10% olive oil, respectively. *Id.* at [0032] and [0035]. Hence, claim 9 of the '254 patent, and claim 13 of the '255 patent are invalid as obvious over the prior art.

5. Claims 11, 19, and 26 of the '254 patent, and claim 16 of the '255 patent are invalid as obvious

Claims 10 and 19 of the '254 patent depend directly on independent claim 1, claim 11 depends directly on claim 10, and claim 26 depends directly on independent claim 22. Likewise, claim 14 of the '255 patent depends directly on independent claim 1 and claim 16 depends on claim 14.

These dependent claims – 11, 19, and 26 of the '254 patent, and claim 16 of the '255 patent – are generally directed to the presence of an alcohol in the claimed emulsion, specifically ethanol for some claims, as a co-surfactant. The alcohol/ethanol is present in the composition in proportions of less than 10% wt/wt or about 2-3 wt/wt %. As discussed above in detail, the compositions of Example 5 and 7 of Zhou contained 3 wt/wt % and 5.5 wt/wt % ethanol, respectively, as a co-surfactant. *Id.* at [0027] and [0032].

Hence, claims 11, 19, and 26 of the '254 patent, and claim 16 of the '255 patent are invalid as obvious over the prior art.

6. <u>Claims 15 and 20 of the '254 patent, and claims 17-19 of the '255 patent are invalid as obvious</u>

Claims 15 and 20 of the '254 patent, and claims 17-19 of the '255 patent depend directly on an independent or a dependent claim which has already been addressed above. For example, claim 15 of the '254 patent depends directly on claim 14, which depends directly on claim 13 that in turn depends on claim 1.

These dependent claims – 15 and 20 of the '254 patent and claims 17-19 of the '255 patent – generally require the composition to comprise sucrose as a tonicity modifier or an osmotic agent and to be present at a concentration of about 3-8 wt/wt % or about 5 wt/wt %.

Zhou discloses the use of sucrose as a protective agent. Zhou at [0010]. *Also*, at 1, claim 1 ("the co-emulsifier is one or several of ethanol ..."). The composition of Example 5 of Zhou was reported to contain 5 wt/wt % glycerin as a protective agent (*i.e.*, a tonicity modifier or an osmotic

agent). *Also*, Example 3 of Zhou provided a composition that contained about 6 wt/wt % of glucose, as an osmotic agent. *Id.* at [0023]. The specification of Zhou further disclosed sucrose as a protective agent and Example 2 specifically described an injectable aprepitant emulsion comprising sucrose. *Id.* at [0010] and [0021]. Thus, claims 15 and 20 of the '254 patent, and claims 17-19 of the '255 patent are invalid as obvious over the prior art.

7. <u>Claim 21 of the '254 patent, and claims 20-21 of the '255 patent are invalid as obvious</u>

Claim 21 of the '254 patent and claims 20-21 of the '255 patent depend either directly or indirectly on independent claim 1 of the respective patents.

These dependent claims generally require the composition to comprise sodium oleate as a pH modifier. Claim 21 of the '255 patent further specifies that the sodium oleate be present at a concentration of about 0.4-0.5 wt/wt %.

The '016 publication mentions the use of a pH adjusting agent in preparing an aprepitant composition. Weng teaches that sodium oleate can function as a co-emulsifier and a buffer. Weng at 1159 ("SO [sodium oleate] had a certain buffering capacity to reduce the pH change to a minimum … Hence, a small amount of SO was often used in commercial parenteral emulsions …"). Likewise, the '777 publication, a reference discussing oil in water emulsion formulations, teaches that sodium oleate can be used in such formulations to adjust the pH of the emulsion to around 8.5. The '777 publication at [0058]. The '520 publication discloses emulsion where a charge stabilizer can act as a buffer, and further mentions sodium oleate, oleic acid as stabilizers. *Id.* at [0009] and [0029]. The '520 publication teaches that "[t]he presence of sodium oleate also has an effect on the pH at which the charge on the emulsion droplets is zero. Emulsions containing sodium oleate reach neutral zeta potential at a lower pH value. These would be expected to be stable over a broader range of pH." *Id.* at [0246].

Moreover, the '520 publication teaches that sodium oleate may be used to stabilize pharmaceutical emulsions. The '520 publication at [0029]. The '520 publication further mentioned the use of sodium oleate in the range of 0.25 to 1.0 wt.%. *Id.* at [0236]-[0247] (Example 8). Thus, claim 21 of the '254 patent, and claims 20-21 of the '255 patent are invalid as obvious over the prior art.

D. <u>Unexpected Results</u>

Defendants contend that no secondary considerations, if any, exist (Defendants await Plaintiff's response to the invalidity contentions on this), that would weigh in favor of non-obviousness with respect to the Asserted Claims of the Two New OB Patents given the strength of the prima facie case of obviousness. Plaintiff bears the burden of production as to any objective indicia, and Defendants assert that Plaintiff cannot meet that burden. Defendants contend that the weight of the probative evidence does not support such indicia; does not establish a nexus between the asserted indicia and the merits of the alleged claimed invention; is not commensurate in scope with the claims; and, in any event, is insufficient in view of the prior art discussed above.

Further, to be probative on the issue of obviousness, there must be a nexus between the evidence of secondary considerations offered and the merits of the claimed invention. *Ormco Corp. v. Align Tech. Inc.*, 463 F.3d 1299, 1312-13 (Fed. Cir. 2006). "[A]ny superior property must be *unexpected* to be considered as evidence of nonobviousness." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007) (emphasis in the original). The party offering "unexpected results" as evidence of non-obviousness is required to provide evidence of the "expected" properties. *See id.* ("Pfizer's evidence must fail because the record is devoid of *any* evidence of what the skilled artisan would have expected.") (emphasis in the original). Furthermore, "[a]lthough secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion." *Id.* at 1372. If the *prima facie* case of obviousness is very strong,

evidence on secondary considerations can prove to be inadequate to overcome it. *See Leapfrog Enterprises, Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

During the prosecution of one of the other patents involved in a separate suit with Defendants, US 9,561,229 ("the '229 patent"), Applicants overcame the Examiner's obviousness rejection by submitting a Declaration by one of the inventors Thomas Ottoboni ("the Ottoboni Declaration"). The Ottoboni Declaration argued that the emulsions disclosed in Zhou were not stable and formed crystals within 4 days of storage at room temperature. Applicants argued that in comparison, Examples 1-3 and 6 of their claimed invention unexpectedly did not form crystals until 2-3 months due to 13 to 15 wt.% of egg yolk lecithin and the ratio of emulsifier to aprepitant. Based on this the Declaration asserted that the "claimed range of *13 to 15 wt.%* egg yolk lecithin results in an unpredictable increase in stability of the claimed pharmaceutical aprepitant emulsion in view of Zhou." The Ottoboni Declaration at 3.

However, the Ottoboni Declaration is deficient for its proposition and the alleged unexpected results described therein are insufficient to overcome the strong showing of *prima facie* obviousness of the Asserted Claims. First, the Declaration did not provide any characterization of the crystalline material that was purportedly observed in Examples 4 and 5 of the specification of the Two New OB Patents to confirm that the crystals were aprepitant and not any other insoluble component, nor did the Ottoboni Declaration provide any repetition to demonstrate reproducibility of the alleged formation of crystals, thereby the Declaration provides an insufficient basis for the conclusion rendered therein. Also, the stability study of Example 7 of the '229 patent demonstrates that each of Examples 1-3 and 6 were stable at room temperature for at least 2 months, or for >10 months under refrigerated conditions. This demonstrates that emulsifier concentrations both inside and outside the claimed range of 13 to 15 wt.% egg yolk

phospholipid demonstrate the alleged "unexpected stability," thereby making any argument regarding the criticality of the range – 13 to 15 wt.%, meritless.

In addition, as discussed above, the use of emulsifiers/surfactants to enhance solubility of poorly water soluble drugs was well-known. Indeed, the '016 publication disclosed that the solubility of aprepitant increases with increasing surfactant concentration. *See* Table 2-5, at [0043] to [0047]. In addition, the prior art specifically taught that the "inclusion of surface-active agents ... may also help to prevent crystal growth." Billany at 337.

Furthermore, Zhou described the aprepitant emulsion disclosed therein as microemulsions and the prior art taught that because of the small droplet size, microemulsions usually require a large emulsifier concentration for stabilization. *See* Mahato at 257 ("[Microemulsions] often contain a *high concentration of the emulsifier(s)* and a cosolvent (such as ethanol)"); Ching-Chiang Su at 150 ("Because of the numerous small droplets, the surface area to volume ratio of microemulsions are very high and it forms easily because of the low surface tension, typically due to *high levels of surface active species*") (emphases added). Given aprepitant was known to be substantially insoluble in both water and oil a POSA would have known that such a compound is likely to stay at the emulsion droplet interface, thereby requiring high interface area and hence increased droplet number. Therefore, given microemulsions were known to have large number of droplets and hence known to require a relatively high concentration of an emulsifier for the stability, a POSA, having encountered any potential precipitation of the drug, would have been motivated to increase the concentration of emulsifier/surfactant beyond what was disclosed in Zhou up to an optimum level to maintain aprepitant in the emulsion and keep the emulsion stable.

Given the known ability of emulsifiers/surfactants to solubilize compounds with poor aqueous solubility, arguments advanced by the Applicants via the Ottoboni Declaration should be

insufficient to overcome obviousness of the claims reciting a slightly higher quantity of surfactant than the prior art. *See Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) ("'[D]ifferences in degree' of a *known and expected* property are *not as persuasive* in rebutting obviousness as differences in 'kind'— i.e., a new property dissimilar to the known property") (emphasis added).

Finally, even assuming, *arguendo*, the Ottoboni Declaration shows an "unpredictable increase in stability" – a fact not conceded by Defendants – the declaration provides no support for a number of Asserted Claims of the Two New OB Patents because the scope of these claims, in terms of the emulsifier concentration, is broader than the 13 to 15 wt.% emulsifier content touted in the declaration. *See e.g.*, claim 6 and 7 of each of the '254 and '255 patents reciting 16, 17 and 18 wt./wt.% of an emulsifier. Additionally, a number of Asserted Claims of the Two New OB Patents lack any reference to the emulsifier content (wt.%) with regard to the total weight of the emulsion and only recite a ratio of the emulsifier to aprepitant. *See e.g.*, all independent claims of the '254 patent. An emulsifier:aprepitant ratio of 20:1 to 25:1 or 23:1 or 24:1 (wt./wt.%) – as recited by these claims – does not inherently fall within the emulsifier content of "13 to 15 wt.%" alleged in the Ottoboni Declaration to have resulted in stable emulsion with no crystallization. For example, 100 g of an aprepitant emulsion containing 0.8 g of aprepitant and 20 g emulsifier would satisfy the emulsifier:aprepitant ratio of 20:1 to 25:1, while falling outside the scope of the emulsifier content of "13 to 15 wt.%." Indeed, Example 3 of the '229 patent illustrates such a scenario (providing an emulsifier:aprepitant ratio of 20:1, while the emulsifier content is 11.7 wt.%). Accordingly, Asserted Claims of the Two New OB Patents reciting only an emulsifier:aprepitant ratio but lacking a limitation for the emulsifier content with regard to the total weight of the emulsion or explicit describing an emulsifier content of outside the 13-15 % wt.

range, are broader in scope and hence not supported by the alleged unexpected results. *In re Peterson,* 315 F.3d at 1330-31 ("showing of unexpected results must be commensurate in scope with the claimed range").

Accordingly, here, there is no evidence of any secondary considerations sufficient to overcome the strong showing of *prima facie* obviousness of any of the Asserted Claims of the Two New OB Patents.

VIII. CLAIMS OF THE TWO NEW OB PATENTS ARE INVALID FOR INDEFINITENESS, LACK OF WRITTEN DESCRIPTION AND/OR LACK OF ENABLEMENT UNDER 35 U.S.C. § 112

A. Legal Standards

1. Indefiniteness

AIA 35 U.S.C. § 112(b) requires that "the specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter" which the inventor/joint inventor regards as the invention. The Supreme Court has held that a patent is invalid for indefiniteness "if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014). A patent claim must be "sufficiently precise to permit a potential competitor to determine whether or not he is infringing." *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470 (Fed. Cir. 1993). Definiteness, like claim construction, is a question of law sometimes involving subsidiary factual determinations. In assessing definiteness, "claims are to be read in light of the patent's specification and prosecution history," and courts apply the "viewpoint of a person skilled in the art at the time the patent was filed." *Nautilus*, 572 U.S. at 908 (alterations and citation omitted).

2. **Written Description**

To satisfy the written description requirement, "the patent specification must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479 (Fed. Cir. 1998) (internal quotations and citation omitted). This means that "the disclosure must . . . convey with reasonable clarity to those skilled in the art that . . . [the inventor] was in possession of the invention." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000) (internal quotations and citation omitted) (affirming district court's finding that the patent claims were invalid); *see also Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005); *In re Curtis*, 354 F.3d 1347, 1350-52 (Fed. Cir. 2004) (affirming Board's finding that a prior application "did not provide an adequate written description of the later-claimed genus of friction enhancing coatings"). Under this requirement, the patent's specification must describe what is claimed with sufficient detail such that a person of ordinary skill in the art can conclude that "the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed Cir. 2010) (citation omitted); *see also Carnegie Mellon Univ. v. Hoffmann–La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008) ("[T]he applicant must 'convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention,' and demonstrate that by disclosure in the specification of the patent." (citation omitted)).

"[T]he hallmark of written description is disclosure. Thus, 'possession as shown in the disclosure' is a more complete formulation." *Ariad*, 598 F.3d at 1351. The test for written description involves an objective inquiry into whether the specification describes the invention sufficiently to allow a person of ordinary skill in the art to understand it and know that the inventor actually invented the claimed invention. *Id*. The operative time for this determination is the date

of the patent's filing. (*Id.* ("The law must be applied to each invention at the time it enters the patent process, for each patented advance has a novel relationship with the state of the art from which it emerges.").) The Federal Circuit has stated that, when determining whether a patent specification complies with the written description requirement:

> The level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology. For generic claims, we have set forth a number of factors for evaluating the adequacy of the disclosure, including "the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue."

Id. (quoting *Capon*, 418 F.3d at 1359).

Significantly, "actual 'possession' or reduction to practice outside of the specification is not enough . . . it is the specification itself that must demonstrate possession." *Id.* at 1352. Finally, it is well established that "a description that merely renders the invention obvious does not satisfy the [written description] requirement." *Id.*

3. <u>Enablement</u>

A patent's specification must describe the invention and "the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same." 35 U.S.C. § 112(a). Whether a claim is enabled under 35 U.S.C. § 112(a) is a question of law. *In re Goodman*, 11 F.3d 1046, 1050 (Fed. Cir. 1993). Also, *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988). The enablement requirement is satisfied when the patent specification enables "those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (citations omitted). The Supreme Court reaffirmed that "the specification must enable the full scope of the invention as defined by its claims," while allowing

for "a reasonable amount of experimentation." *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610-12 (2023). A patent claim is invalid for lack of enablement if the specification fails to teach those in the art how to make and use the invention as broadly as it is claimed without undue experimentation. *Warner Lambert Co. v. Teva Pharms. USA, Inc.,* 418 F.3d 1326, 1337 (Fed. Cir. 2005); *see also In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993) ("Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'") (internal citations omitted).

B. Asserted Claims 1, 5-7, 9, 11, 15, 19-22, 24, 26-27, and 29 of the '254 patent and claims 1, 5-11, 13, and 16-30 of the '255 patent allowing an emulsifier concentration outside of 13-15% fail to satisfy the written description

Claims 1, 5, 9, 11, 15, 19-22, 24, 26-27, and 29 of the '254 patent and claim 30 of the '255 patent recite emulsifier content as a ratio of emulsifier to aprepitant, not as the absolute amount of the emulsifier in the composition. For example, claim 30 of the '255 patent requires, among other things, "about 0.7-0.8 wt % aprepitant," "an egg phospholipid emulsifier," "wherein the ratio of the emulsifier to aprepitant is about 20:1 to 25:1." Based on the recited aprepitant content (about 0.7-0.8 wt/wt.%) and the emulsifier to aprepitant ratio (ranging from about 20:1 to 25:1), these claims allow for more than 15 wt.% emulsifier in the composition.

Additionally, claims 6-7 of the '254 patent and claims 1, 5-11, 13, and 16-29 of the '255 patent specifically require an emulsifier concentration that is greater than 15 wt/wt.%. However, based on the four corners of the specification a POSA could not reasonably conclude that the Applicants actually possessed an injectable aprepitant emulsion containing more than 15 wt./wt.% emulsifier.

During the prosecution of the '742 patent (the parent of the '254 and '255 patents), in an Office Action, dated April 6, 2017 (hereinafter, "'742 First Office Action"), the Examiner rejected

the pending claims as obvious over Zhou pursuant to 35 U.S.C. § 103(a), alone or in combination with additional prior references. '742 Patent First Office Action, p. 4. [3]

In response, Applicants directed the Examiner to the Ottoboni Declaration, submitted September 1, 2016, in the application that eventually issued as the '229 patent, in which "Dr. Ottoboni confirmed that Example 4 of the instant application describes an emulsion that was prepared according to the methods taught by Zhou." '742 Patent Applicants' Response, at p. 8. The Applicants argued that Example 4 was unsuccessful as it resulted in the eventual formation of crystals. *Id.* The Applicants contrasted Example 4 with successful example formulations in the specification: "the formulations of Examples 1, 2, 3 and 6 with increased amount of the emulsifier were stable at room temperature for at least 2 months in the case of Examples 1, 3 and 6, and for at least 3 months for Example 2." *Id.* at p. 8. The Applicants relied on the foregoing to conclude that "[n]either Zhou nor Booth recognizes the formation of crystals in the emulsions produced as described in each of their references or the *effects of 13 to 15 weight percent emulsifier* on stability of an emulsion." *Id.* (emphasis added). *Also*, at p. 9 ("As discussed above, the stability of an emulsion comprising an emulsifier in the the [sic] amount in accordance with the current claims is much improved compared to prior art emulsions comprising the emulsifier in an amount outside

[3] As discussed *supra*, the '742 patent is the parent of the '254 patent and the '255 patent and accordingly, the prosecution history of the '742 patent is considered intrinsic evidence for purposes of claim construction. *See Biosig Instruments*, 783 F.3d at 1378 ("claim construction involves consideration of primarily the intrinsic evidence, *viz.*, the claim language, the specification, and the prosecution history") (quoting *Enzo*, 599 F.3d at 1332). *See Augustine Med.*, 181 F.3d at 1300 ("Because the prosecution history of a parent application may limit the scope of a *later application* using the *same claim term* … these claim amendments and arguments restrict the scope of the claims in each of the *later issued patents* containing the [same] limitation.") (internal citation omitted) (emphasis added); *see also Omega Eng'g*, 334 F.3d at 1333 ("[A]n interpretation asserted in the prosecution of a parent application can also affect … continuation-in-part applications" (*citing Wang Labs., Inc. v. Am. Online Inc.,* 197 F.3d 1377, 1384 (Fed. Cir. 1999))).

the scope of the current claims. The improved stability cannot be predicted.") (citing the Ottoboni Declaration).

The '742 Patent Notice of Allowability, dated March 12, 2018, specifically relied on these statements regarding Applicants' assertion of unexpected results, concluding: "the claimed injectable formulations exhibit surprising and unexpected properties compared to the emulsions of Zhou." '742 Patent Notice of Allowability, pp. 5-6. The Examiner also expressly made the Ottoboni Declaration "of record" in the '742 patent file history. '742 Patent Notice of Allowability, pp. 5-6.

The examples in the common specification of the '742 patent family (which includes the '254 and '255 patents) align with the assertions in the Ottoboni declaration – that the work of the inventors was solely focused on formulations that contained 15 wt/wt % or less of emulsifier. *See* '254 patent Examples 1, 2, 3 and 6. There is no evidence that the inventors possessed an aprepitant emulsion having more than 15 wt% emulsifier. The common specification's only reference to a higher than 15 wt./wt.% of emulsifier appears in a rather broad generic statement that also includes the prior art emulsifier concentration (10 wt./wt.%) and provides no guidance or affirmation whether all of those stated emulsifier concentrations would result in a stable emulsion. *See e.g.*, the '254 patent, col. 3, ll. 49-52 ("In some embodiments, the composition comprises about 10 wt/wt% to 20 wt/wt%, 12 wt/wt% to 17 wt/wt%, 13 wt/wt% to 16 wt/wt%, 13 wt/wt% to 15 wt/wt%, 14 wt/wt % to 15 wt/wt %, or 13 wt/wt % to 14 wt/wt % emulsifier"). Indeed, the Ottoboni declaration makes it clear they did not obtain such success as the critical and unexpected results of the alleged invention were expressly tied to 13-15 wt/wt% of emulsifier.

Accordingly, the common specifications of the '254 and '255 patents do not "reasonably convey to a person of ordinary skill in the art" that Heron had possession of a stable injectable

aprepitant emulsion containing an emulsifier concentration *outside* of the 13-15% range, as contemplated by these claims. *See FWP IP ApS v. Biogen MA, Inc.*, 749 F. App'x 969, 972, 974-976 (Fed. Cir. 2018) (claims to a method of treating multiple sclerosis with a therapeutically effective dosage of 480 mg/day lacked sufficient written description, where 480 mg was disclosed only twice in a paragraph teaching possible daily dosages and once as an interim dose in an up-scale table, because "the up-scale table does not discuss therapeutically effective dosages at all, much less the specific dosage of 480 mg of fumarates per day as being therapeutically effective for treating MS"). *See also, Nuvo Pharms. (Ir.) Designated Activity Co. v. Dr. Reddy's Labs. Inc.* 923 F.3d 1368 at 1380 (Fed. Cir. 2019) ("We have expressly rejected the argument that the written description requirement ... is necessarily met as a matter of law because the claim language appears in *ipsis verbis* in the specification." (*citing Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 968 (Fed. Cir. 2002); internal quotation marks omitted)). "[T]he purpose of the written description requirement is to 'ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification.'" *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 906, 920 (Fed. Cir. 2004) (quoting *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed. Cir. 2000)).

Accordingly, claims 1, 5-7, 9, 11, 15, 19-22, 24, 26-27, and 29 of the '254 patent and claims 1, 5-11, 13, and 16-30 of the '255 patent are invalid under 35 U.S.C. § 112(a) for lack of written description.

C. <u>Claims 1, 5-7, 9, 11, 15, 19-22, 24, 26-27, and 29 of the '254 patent and claims 1, 5-11, 13, and 16-30 of the '255 patent allowing an emulsifier concentration outside of 13-15% are not enabled</u>

As discussed above, claims 1, 5-7, 9, 11, 15, 19-22, 24, 26-27, and 29 of the '254 patent and claims 1, 5-11, 13, and 16-30 of the '255 patent are invalid as obvious since a POSA would have arrived at the claimed invention as a matter of routine experimentation in light of the prior

art. Alternatively, to the extent Heron contends that these claims are not obvious, then claims 1, 5-7, 9, 11, 15, 19-22, 24, 26-27, and 29 of the '254 patent and claims 1, 5-11, 13, and 16-30 of the '255 patent necessarily are invalid for lack of enablement.

The scope of some of these asserted claims of the '254 and '255 patents include numerous embodiments that render the claims invalid due to failure to satisfy the enablement requirement. As explained above, all of these claims of the '254 and '255 patent allow for inclusion of more than 15 wt/wt% of emulsifier in the claimed composition.

As discussed above, during the prosecution of the ancestor '742 patent, Heron identified an emulsifier concentration range of 13-15 wt/wt % that was alleged to be unexpected and critical to the invention in that it provided stability for at least 1 week. Thus, Heron itself implicitly acknowledged that any formulation with a concentration of emulsifier outside the range of 13-15 wt/wt% may be unstable, and did not identify any known pathway for a skilled artisan to enhance the stability of a formulation with an emulsifier concentration outside the range of 13-15 wt/wt%.

The Federal Circuit developed a framework with a set of guidelines in *In re Wands*, referred to as the *Wands* factors, to evaluate compliance with the enablement requirement of 35 U.S.C. 112(a). The *Wands* factors include: 1) the quantity of experimentation necessary; 2) the amount of direction or guidance presented; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. *In re Wands*, 858 F.2d at 737.

A large amount of experimentation is necessary to arrive at a stable emulsion containing more than 15 wt/wt% concentration of emulsifier. The examples in the specification of the '254

and '255 patents that allegedly did not result in the formation of a precipitate do not provide any direction of guidance about aprepitant formulations that would demonstrate the purported stability of a formulation with more than 15 wt/wt% emulsifier since the highest emulsifier concentration contemplated by these examples is 14.3 wt./wt.%. *See*, *e.g.*, '254 patent at Examples 1, 2, 3 and 6. There is no teaching in the specification of adjustments to be made to the formulations to successfully prepare emulsions with the claimed emulsifier concentrations >15 wt/wt% in the '254 and '255 patents. Additionally, the nature of the invention is complex and the state of the prior art, weighs in favor of lack of enablement because the prior art did not disclose a stable aprepitant emulsion having greater than 15 wt/wt% of emulsifier. Further, the breadth of the claims weighs in favor of no enablement at least because the claims are broad enough as they cover an emulsifier concentration >15 wt/wt%.

Thus, the claimed embodiments that have concentrations of emulsifier outside the scope of 13-15 wt/wt% (*e.g.* 16-20%) are inoperable and cannot be salvaged no matter the amount of experimentation. The presence of numerous inoperable embodiments within the scope of the claims would require a POSA to experiment unduly and, according to Heron, those experiments would yield nothing but failed efforts. The specification does not indicate otherwise. Accordingly, for at least these reasons claims 1, 5-7, 9, 11, 15, 19-22, 24, 26-27, and 29 of the '254 patent and claims 1, 5-11, 13, and 16-30 of the '255 patent are invalid for lack of enablement.

D. <u>Claims 1, 5-7, 9, 11, 15, 19-22, 24, 26-27, and 29 of the '254 patent and claims 8-11, 24, and 27-30 of the '255 patent having a ratio of emulsifier to aprepitant outside 18:1-22:1 are invalid for lack of enablement</u>

As discussed above, claims 1, 5-7, 9, 11, 15, 19-22, 24, 26-27, and 29 of the '254 patent and claims 8-11, 24, and 27-30 of the '255 patent are invalid as obvious since a POSA would have arrived at the claimed invention as a matter of routine experimentation in light of the prior

art. Alternatively, to the extent Heron contends that these claims are not obvious, then claims 1, 5-7, 9, 11, 15, 19-22, 24, 26-27, and 29 of the '254 patent and claims 8-11, 24, and 27-30 of the '255 patent necessarily are invalid for lack of enablement.

The scope of some of these asserted claims of the '254 and '255 patents include numerous inoperable embodiments that render the claims invalid due to failure to satisfy the enablement requirement. For example, claims 1, 5-7, 9, 11, 15, and 19-21 of the '254 patent require an emulsifier to aprepitant ratio of 20:1 to 25:1 (wt/wt%), claims 22, 24, and 26 of the '254 patent require a ratio of emulsifier to aprepitant of 23:1 (wt/wt%), while claims 27 and 29 of the '254 patent require a corresponding ratio of 24:1 (wt/wt%). Claims 8, 24, and 30 of the '255 patent require a ratio of emulsifier to aprepitant of 20:1-25:1, while claims 9-11 and 27-29 of the '255 patent require specific ratios of 23:1, or 24:1, or 25:1.

As discussed above, during the prosecution of the ancestor, the '742 patent, Heron identified a ratio range of emulsifier to aprepitant (18:1-22:1) that was alleged to be unexpected and critical to the invention as it provided stability for at least 1 week. Thus, Heron itself contends that any formulation having a ratio of emulsifier to aprepitant outside the ratio of 18:1-22:1 will not be stable, and inherently Heron has admitted that there is no known pathway for a skilled artisan to enhance stability of the formulation other than implementing the ratio of 18:1-22:1.

The examples in the specification of the '254 and '255 patents that allegedly did not result in the formation of a precipitate do not provide reasonable clarity as to ratios other than 20:1 because every single one of these examples is limited to an emulsifier to aprepitant ratio of 20:1. *See* the '254 patent Examples 1, 2, 3 and 6. There is no teaching in the specification as to what adjustments to the compositions should be considered to successfully prepare emulsions with the

claimed concentrations above 22:1, as claimed in the '254 and '255 patents. As discussed above in connection with the claims covering greater than 15 wt/wt% of emulsifier, the *Wands* factors in this case also weigh in favor of lack of enablement.

Thus, according to Heron's arguments and admissions, the claimed embodiments that have ratios of emulsifier to aprepitant outside the scope of 18:1-22:1 (*e.g.* 23:1-25:1) are inoperable and cannot be salvaged no matter the amount of experimentation. The presence of numerous inoperable embodiments within the scope of the claims would require a POSA to experiment unduly and, according to Heron, those experiments would yield nothing but failed efforts. The specification does not indicate otherwise. Accordingly, for at least these reasons claims 1, 5-7, 9, 11, 15, 19-22, 24, 26-27, and 29 of the '254 patent and claims 8-11, 24, and 27-30 of the '255 patent are invalid for lack of enablement.

E. <u>All Asserted Claims of the Two New OB Patents reciting emulsifier content or emulsifier to aprepitant ratio by weight are invalid as indefinite</u>

All asserted claims of the '254 and '255 patents specify an emulsifier content in the claimed composition, either through absolute concentration of the emulsifier (wt./wt.%) or *via* an emulsifier to aprepitant ratio (wt./wt.%). The asserted claims of the '254 and '255 patents are invalid as indefinite to the extent anything other than the measured weight of the emulsifier used to prepare the claimed emulsion is utilized to refer to the weight percentage of the emulsifier specified by the asserted claims.[4]

[4] While the specifications of the Two New OB Patents state that the composition described by the alleged invention comprises 'about' 10-20% w/w of emulsifier, and the term "about" is defined to mean "±5%, ±10%, or ±20% of the value being modified" – this provides no clarification and is therefore insufficient to cure the indefiniteness issues.

The examples in the '254 and '255 patents leading to purportedly stable aprepitant formulations show that the wt/wt% of egg yolk content is calculated based on the amount of Lipoid E 80 added to the experimental formulation. For example:

TABLE 1

Component	Amount (g)	Concentration (w/w %)	Ratio to Aprepitant
Aprepitant	0.750	0.679	1
Lipoid E 80	15.0	13.6	20
Soybean Oil	10.0	9.05	13.3
Ethanol[1]	8.59	7.78	11.5
Sucrose	5.60	5.07	7.5
Sodium Oleate	0.500	0.453	0.667
Water for Injection	70.0	63.4	93.3
Total	110	100	—

[1]Final amount after taking into account the ethanol that was evaporated during processing.

The '254 patent at 20:5-17; the '255 patent at 20:5-17 (same). Lipoid E 80 is included as the egg lecithin component of the experimental formulations and in the above example the inventor added 15 grams of the commercial Lipoid E 80 product. *See* the '254 patent at 20:5-17. 15 g of Lipoid E 80 is precisely 13.6 w/w % of the 110 gram total weight of the experimental formulation. Thus, a POSA reviewing the common specification of the '254 and '255 patents would expect that the basis for determining the scope of the alleged invention would be calculating the w/w% concentration of emulsifier based on the weight of the Lipoid E 80 used in the proposed pharmaceutical formulation.

Accordingly, the asserted claims of the '254 and '255 patents are invalid for indefiniteness since these claims, fail to inform a POSA with "reasonable certainty" as to the scope of the invention regarding the emulsifier content (wt/wt %) of the emulsion, if the said content signifies anything other than the amount of emulsifier used to prepare the emulsion. As noted above, examples in the '254 and '255 patents calculate the w/w% of egg lecithin and its ratio against aprepitant, in the formulations based on the weight of the Lipoid E 80 used in the experimental

formulations. *See*, *e.g.*, the '254 patent at 20:5-17 (Table 1). There is no disclosure that the inventors considered anything other than the measured weight of the commercial Lipoid E 80 product when calculating the w/w% of egg lecithin and its relative proportion against aprepitant in the formulation.

Accordingly, to the extent the emulsifier content recited by the asserted claims of the '254 and '255 patents refer to anything other than the measured weight of the emulsifier used to prepare the claimed emulsion, the asserted claims of the '254 and '255 patents would lack the objective boundaries required under § 112(b) because these claims, read in light of the specification and the prosecution history, provide no discernable standard for a POSA to identify when an aprepitant emulsion composition having a specific emulsifier content would be considered infringing on the basis of the percentage of emulsifier or its ratio against aprepitant as recited by these claims. *See Media Rights Techs., Inc. v. Capital One Fin. Corp.*, 800 F.3d 1366, 1371 (Fed. Cir. 2015) ("[A] claim is indefinite if its language might mean several different things and no informed and confident choice is available among the contending definitions") (quoting *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 911 at n.8) (internal quotation marks omitted).

F. <u>Claims 22, 24, 26, 27 and 29 of the '254 patent Are Indefinite</u>

Asserted independent claims 22 and 27 of the '254 patent and all asserted claims depending therefrom, are indefinite. Claim 22 of the '254 patent requires "wherein the ratio of the emulsifier to aprepitant ranges about 23:1 (wt/wt%)" and claim 27 of the '254 patent requires "wherein the ratio of the emulsifier to aprepitant ranges about 24:1 (wt/wt%)." Because both claims provide a single fixed numerical point, the inclusion of the word "ranges" renders the claims indefinite as a POSA cannot determine with reasonable certainty the scope of the claims. Accordingly, claims 22, 24, 26, 27 and 29 of the '254 patent are indefinite.

IX. CLAIM CHARTS

Slayback includes the following attachments containing claim charts specifically identifying where claim limitations are found in the identified prior art references:

Attachment K – U.S. Patent No. 12,115,254

Attachment L – U.S. Patent No. 12,115,255

References within these to Attachments A-J reference the previously served attachments to Slayback's contentions in C.A. No. 24-cv-830 on October 18, 2024.

X. DOCUMENT PRODUCTION

Pursuant to Paragraph 4(d) of the Delaware Default Standard for Discovery, Defendants state that they already served a document production (SLAY-APREP0009700 to SLAY-APREP0010517 and SLAY-APREP0010554 to SLAY-APREP0010595) via electronic means on October 18, 2024, in connection with the service of Slayback's invalidity contentions.

Dated: January 13, 2025

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Attachment K – Claim Chart for U.S. Patent No. 12,115,254

Claim Element		Identification of Prior Art Anticipating or Rendering Claim Element Obvious
1[a].	An injectable pharmaceutical emulsion comprising:	*See* discussion of Claim 1[a] of Attachment A – Claim Chart for the '229 patent.
1[b].	about 0.7-0.8 wt % aprepitant;	*See* discussion of Claim 1[b] of Attachment A – Claim Chart for the '229 patent.
1[c].	an emulsifier;	*See* discussion of Claim 1[c] of Attachment A – Claim Chart for the '229 patent.
1[d].	an oil;	*See* discussion of Claim 1[d] of Attachment A – Claim Chart for the '229 patent.
1[e].	a co-surfactant; and	*See* discussion of Claim 6[b] of Attachment A – Claim Chart for the '229 patent.
1[f].	water,	*See* discussion of Claim 1[i] of Attachment B – Claim Chart for the '465 patent.
1[g].	wherein the ratio of the emulsifier to aprepitant ranges from about 20:1 to 25:1 (wt/wt %).	*See* discussion of Claim 1[j] of Attachment B – Claim Chart for the '465 patent.
5[a].	The emulsion of claim **1,**	*See* claim 1.

Claim Element		Identification of Prior Art Anticipating or Rendering Claim Element Obvious
5[b].	wherein the emulsifier is an egg lecithin.	*See* discussion of Claim 1[c] of Attachment A – Claim Chart for the '229 patent.
6[a].	The emulsion of claim **5,**	*See* claim 5.
6[b].	wherein the egg lecithin is present in the emulsion at about 16 wt/wt %.	*See* discussion of Claim 1[c] of Attachment A – Claim Chart for the '229 patent.
7[a].	The emulsion of claim **1,**	*See* claim 1.
7[b].	wherein the egg lecithin is present in the emulsion at about 17 wt/wt %.	*See* discussion of Claim 1[c] of Attachment A – Claim Chart for the '229 patent.
9[a].	The emulsion of claim **8**,	*See* claim 8.
9[b].	wherein the oil is present at a concentration of about 9 wt/wt % to 10 wt/wt %.	*See* discussion of Claim 1[d] of Attachment A – Claim Chart for the '229 patent.
11[a].	The emulsion of claim **10**,	*See* claim 10.

Claim Element		Identification of Prior Art Anticipating or Rendering Claim Element Obvious
11[b].	wherein the alcohol is present in the emulsion at less than 10 wt/wt %.	*See* discussion of Claim 6[b] of Attachment A – Claim Chart for the '229 patent.
15[a].	The emulsion of claim **14**,	*See* claim 14.
15[b].	wherein the osmotic agent is present at a concentration of about 3 wt/wt % to 8 wt/wt %.	*See* discussion of Claim 4[b] of Attachment A – Claim Chart for the '229 patent.
19[a].	The emulsion of claim **1**,	*See* claim 1.
19[b].	wherein the co-surfactant is ethanol.	*See* discussion of Claim 6[b] of Attachment A – Claim Chart for the '229 patent.
20[a].	The emulsion of claim **1**,	*See* claim 1.
20[b].	further comprising sucrose.	*See* discussion of Claim 4[b] of Attachment A – Claim Chart for the '229 patent.
21[a].	The emulsion of claim **1**,	*See* claim 1.

Claim Element		Identification of Prior Art Anticipating or Rendering Claim Element Obvious
21[b].	further comprising sodium oleate.	*See* discussion of Claim 1[e] of Attachment A – Claim Chart for the '229 patent.
22[a].	An injectable pharmaceutical emulsion comprising:	*See* discussion of Claim 1[a] of Attachment A – Claim Chart for the '229 patent.
22[b].	about 0.7-0.8 wt % aprepitant;	*See* discussion of Claim 1[b] of Attachment A – Claim Chart for the '229 patent.
22[c].	an emulsifier;	*See* discussion of Claim 1[c] of Attachment A – Claim Chart for the '229 patent.
22[d].	an oil;	*See* discussion of Claim 1[d] of Attachment A – Claim Chart for the '229 patent.
22[e].	a co-surfactant; and	*See* discussion of Claim 6[b] of Attachment A – Claim Chart for the '229 patent.
22[f].	water,	*See* discussion of Claim 1[i] of Attachment B – Claim Chart for the '465 patent.
22[g].	wherein the ratio of the emulsifier to aprepitant ranges about 23:1 (wt/wt %).	*See* discussion of Claim 1[j] of Attachment B – Claim Chart for the '465 patent.

Claim Element		Identification of Prior Art Anticipating or Rendering Claim Element Obvious
24[a].	The emulsion of claim **23**,	*See* claim 23.
24[b].	wherein the phospholipid is selected from the group consisting of egg phospholipids and soy phospholipids.	*See* discussion of Claim 1[c] of Attachment A – Claim Chart for the '229 patent.
26[a].	The emulsion of claim **22**,	*See* claim 22.
26[b].	wherein the co-surfactant comprises an alcohol present in the emulsion at less than 10 wt/wt %.	*See* discussion of Claim 6[b] of Attachment A – Claim Chart for the '229 patent.
27[a].	An injectable pharmaceutical emulsion, comprising:	*See* discussion of Claim 1[a] of Attachment A – Claim Chart for the '229 patent.
27[b].	about 0.7-0.8 wt % aprepitant;	*See* discussion of Claim 1[b] of Attachment A – Claim Chart for the '229 patent.
27[c].	an emulsifier;	*See* discussion of Claim 1[c] of Attachment A – Claim Chart for the '229 patent.

Claim Element		Identification of Prior Art Anticipating or Rendering Claim Element Obvious
27[d].	an oil;	*See* discussion of Claim 1[d] of Attachment A – Claim Chart for the '229 patent.
27[e].	a co-surfactant; and	*See* discussion of Claim 6[b] of Attachment A – Claim Chart for the '229 patent.
27[f].	water,	*See* discussion of Claim 1[i] of Attachment B – Claim Chart for the '465 patent.
27[g].	wherein the ratio of the emulsifier to aprepitant ranges about 24:1 (wt/wt %).	*See* discussion of Claim 1[j] of Attachment B – Claim Chart for the '465 patent.
29[a].	The emulsion of claim **27**,	*See* claim 27.
29[b].	wherein the phospholipid is selected from the group consisting of egg phospholipids and soy phospholipids.	*See* discussion of Claim 1[c] of Attachment A – Claim Chart for the '229 patent.

Attachment L – Claim Chart for U.S. Patent No. 12,115,255

Claim Element		Identification of Prior Art Anticipating or Rendering Claim Element Obvious
1[a].	An injectable emulsion, comprising:	*See* discussion of Claim 1[a] of Attachment A – Claim Chart for the '229 patent.
1[b].	0.7-0.8 wt % aprepitant;	*See* discussion of Claim 1[b] of Attachment A – Claim Chart for the '229 patent.
1[c].	13 wt/wt % to 20 wt/wt % of an emulsifier;	*See* discussion of Claim 1[c] of Attachment A – Claim Chart for the '229 patent.
1[d].	an oil;	*See* discussion of Claim 1[d] of Attachment A – Claim Chart for the '229 patent.
1[e].	a co-emulsifier which is an alcohol;	*See* discussion of Claim 6[b] of Attachment A – Claim Chart for the '229 patent.
1[f].	a tonicity modifier;	*See* discussion of Claim 4[b] of Attachment A – Claim Chart for the '229 patent.
1[g]	a pH modifier; and	*See* discussion of Claim 1[e] of Attachment A – Claim Chart for the '229 patent.
1[h]	water;	*See* discussion of Claim 1[i] of Attachment B – Claim Chart for the '465 patent.
1[i]	wherein the pH of the emulsion ranges from about 7.5 to 9.0.	*See* discussion of Claim 1[f] of Attachment A – Claim Chart for the '229 patent.

Claim Element		Identification of Prior Art Anticipating or Rendering Claim Element Obvious
5[a].	The emulsion of claim **1,**	*See* claim 1.
5[b].	wherein the emulsifier is an egg lecithin.	*See* discussion of Claim 1[c] of Attachment A – Claim Chart for the '229 patent.
6[a].	The emulsion of claim **5,**	*See* claim 5.
6[b].	wherein the egg lecithin is present in the emulsion at about 17 wt/wt %.	*See* discussion of Claim 1[c] of Attachment A – Claim Chart for the '229 patent.
7[a].	The emulsion of claim **5,**	*See* claim 5.
7[b].	wherein the egg lecithin is present in the emulsion at about 18 wt/wt %.	*See* discussion of Claim 1[c] of Attachment A – Claim Chart for the '229 patent.
8[a].	The emulsion of claim **5**,	*See* claim 5.
8[b].	wherein the ratio of egg lecithin to aprepitant is between about 20:1 to 25:1.	*See* discussion of Claim 1[j] of Attachment B – Claim Chart for the '465 patent.

Claim Element		Identification of Prior Art Anticipating or Rendering Claim Element Obvious
9[a].	The emulsion of claim **5**,	*See* claim 5.
9[b].	wherein the ratio of egg lecithin to aprepitant is about 23:1.	*See* discussion of Claim 1[j] of Attachment B – Claim Chart for the ‘465 patent.
10[a].	The emulsion of claim **5**,	*See* claim 5.
10[b].	wherein the ratio of egg lecithin to aprepitant is about 24:1.	*See* discussion of Claim 1[j] of Attachment B – Claim Chart for the ‘465 patent.
11[a].	The emulsion of claim **5**,	*See* claim 5.
11[b].	wherein the ratio of egg lecithin to aprepitant is about 25:1.	*See* discussion of Claim 1[j] of Attachment B – Claim Chart for the ‘465 patent.
13[a].	The emulsion of claim **12**,	*See* claim 12.
13[b].	wherein the soybean oil is present at a concentration of about 9 wt/wt % to 10 wt/wt %.	*See* discussion of Claim 1[d] of Attachment A – Claim Chart for the ‘229 patent.

Claim Element		Identification of Prior Art Anticipating or Rendering Claim Element Obvious
16[a].	The emulsion of claim **14**,	*See* claim 14.
16[b].	wherein the ethanol nis present in the emulsion at a concentration of about 2 wt/wt % to 3 wt/wt %.	*See* discussion of Claim 4[b] of Attachment A – Claim Chart for the '229 patent.
17[a].	The emulsion of claim **1**,	*See* claim 1.
17[b].	wherein the tonicity modifier in the emulsion is sucrose.	*See* discussion of Claim 4[b] of Attachment A – Claim Chart for the '229 patent.
18[a].	The emulsion of claim **16**,	*See* claim 16.
18[b].	wherein the sucrose is present at a concentration of about 3 wt/wt % to 8 wt/wt %.	*See* discussion of Claim 4[b] of Attachment A – Claim Chart for the '229 patent.
19[a].	The emulsion of claim **16**,	*See* claim 16.
19[b].	wherein the sucrose is present at a concentration of about 5 wt/wt %.	*See* discussion of Claim 4[b] of Attachment A – Claim Chart for the '229 patent.

Claim Element		Identification of Prior Art Anticipating or Rendering Claim Element Obvious
20[a].	The emulsion of claim **1**,	*See* claim 1.
20[b].	wherein the pH modifier in the emulsion is sodium oleate.	*See* discussion of Claim 1[e] of Attachment A – Claim Chart for the '229 patent.
21[a].	The emulsion of claim **19**,	*See* claim 19.
21[b].	wherein the sodium oleate is present at a concentration of about 0.4 wt/wt % to 0.5 wt/wt %.	*See* discussion of Claim 9[b] of Attachment J – Claim Chart for the '800 patent.
22[a].	The emulsion of claim **1**,	*See* claim 1.
22[b].	wherein the aprepitant is present in the emulsion at about 0.7 wt/wt %.	*See* discussion of Claim 1[b] of Attachment A – Claim Chart for the '229 patent.
23[a].	The emulsion of claim **21**,	*See* claim 21.

Claim Element		Identification of Prior Art Anticipating or Rendering Claim Element Obvious
23[b].	wherein the phospholipid is egg lecithin.	*See* discussion of Claim 1[c] of Attachment A – Claim Chart for the '229 patent.
24[a].	The emulsion of claim **21**,	*See* claim 21.
24[b].	wherein the ratio of phospholipid to aprepitant is between about 20:1 to 25:1.	*See* discussion of Claim 1[j] of Attachment B – Claim Chart for the '465 patent.
25[a].	The emulsion of claim **21**,	*See* claim 21.
25[b].	wherein the phospholipid is present at a concentration of about 17 wt/wt %.	*See* discussion of Claim 1[c] of Attachment A – Claim Chart for the '229 patent.
26[a].	The emulsion of claim **21**,	*See* claim 21.
26[b].	wherein the phospholipid is present at a concentration of about 18 wt/wt %.	*See* discussion of Claim 1[c] of Attachment A – Claim Chart for the '229 patent.

Claim Element		Identification of Prior Art Anticipating or Rendering Claim Element Obvious
27[a].	The emulsion of claim **21**,	*See* claim 21.
27[b].	wherein the ratio of phospholipid to aprepitant is about 23:1.	*See* discussion of Claim 1[j] of Attachment B – Claim Chart for the '465 patent.
28[a].	The emulsion of claim **21**,	*See* claim 21.
28[b].	wherein the ratio of phospholipid to aprepitant is about 24:1.	*See* discussion of Claim 1[j] of Attachment B – Claim Chart for the '465 patent.
29[a].	The emulsion of claim **21**,	*See* claim 21.
29[b].	wherein the ratio of phospholipid to aprepitant is about 25:1.	*See* discussion of Claim 1[j] of Attachment B – Claim Chart for the '465 patent.
30[a].	An injectable pharmaceutical emulsion, comprising:	*See* discussion of Claim 1[a] of Attachment A – Claim Chart for the '229 patent.
30[b].	about 0.7-0.8 wt % aprepitant;	*See* discussion of Claim 1[b] of Attachment A – Claim Chart for the '229 patent.

Claim Element		Identification of Prior Art Anticipating or Rendering Claim Element Obvious
30[c].	an egg phospholipid emulsifier;	*See* discussion of Claim 1[c] of Attachment A – Claim Chart for the '229 patent.
30[d].	an oil;	*See* discussion of Claim 1[d] of Attachment A – Claim Chart for the '229 patent.
30[e].	a co-surfactant.	*See* discussion of Claim 6[b] of Attachment A – Claim Chart for the '229 patent.
30[f].	water; and	*See* discussion of Claim 1[i] of Attachment B – Claim Chart for the '465 patent.
30[g].	a pH modifier,	*See* discussion of Claim 1[e] of Attachment A – Claim Chart for the '229 patent.
30[h].	wherein the ratio of the emulsifier to aprepitant is about 20:1 to 25:1 (wt/wt %).	*See* discussion of Claim 1[j] of Attachment B – Claim Chart for the '465 patent.